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ANNALS OF
INTERNAL MEDICINE

VOLUME 28 JANUARY 1948 NUMBER 1

THE PATHOGENESIS OF LUPUS ERYTHEMATOSUS AND ALLIED CONDITIONS *

By PAUL KLEMPERER, M.D., *New York, N. Y.*

IN 1872 when Kaposi [1] published his first report of acute lupus erythematosus, medicine was still dominated by the pathologic-anatomic doctrine that disease is the result of alterations of bodily structure. Today the study of pathogenesis aims at a full comprehension and integration of all the factors of the external and internal environment which bring about that altered state of life, called disease. Inquiry into the genesis of a disease can no longer be content with the mere perception of structural alterations. Yet the definition of most maladies still depends upon an exact knowledge of characteristic organ and tissue changes. Therefore, the student of pathologic anatomy can still make his worthwhile contribution to pathogenesis. The history of our knowledge of acute lupus erythematosus readily supports the thesis that anatomic pathology can clarify *some* problems of a puzzling disease and might be able to guide an inquiry into its fundamental nature.

Kaposi's original description of acute lupus erythematosus referred to some of the extracutaneous symptoms of the disease. Subsequent dermatologic investigators added further observations, which were well summarized by Jadassohn [2] at the turn of the century. Nevertheless it was generally accepted that acute lupus erythematosus was merely a cutaneous disease. The general constitutional symptoms such as fever, prostration, typhoid state, as well as the local morbid phenomena such as joint pain and swelling, ulcerations of mucous membranes, glandular swelling and albuminuria were vaguely interpreted as the manifestations of a severe "toxic" state induced by the severe involvement of the skin. Autopsy reports of this period mentioned the occurrence of pneumonia and pleuritis, parenchymatous nephritis, occasionally tuberculosis and degeneration of the parenchymatous

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From the Laboratories, Division of Pathology, The Mount Sinai Hospital, New York, N. Y.

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organs. Pernet [3] referred to small vegetations on the mitral valve in his case. In the question of etiology, main emphasis was placed upon the rôle of tuberculosis. Indeed, up to recent years the tuberculous etiology of acute lupus erythematosus has been seriously considered; finally it was disproved by Keil.[4] During the first two decades of this century, an increasing number of well observed cases was reported by competent clinicians from the broader viewpoint of internal medicine (Goeckerman,[5] Keefer and Felty [6]). Acute lupus erythematosus thus came to be recognized as a clinical entity in which the cutaneous lesions were merely part of a serious systemic malady. However, attempts to define the disease in terms of morbid anatomy were less successful because the observations at autopsy were not characteristic and mostly disclosed only the terminating events of a grave systemic disorder. Libman and Sacks' [7] report of an unusual form of endocarditis in cases with the characteristic clinical symptom complex constitutes the first significant contribution to the comprehension of the morbid anatomy of acute lupus erythematosus. Subsequently these observations were confirmed and amplified by Gross (1932 [8] and 1940 [9]). These disclosures indicated that lupus erythematosus should be defined anatomically as a primary cardiac disease. In 1935, Baehr, Klemperer and Schifrin [10] called attention to conspicuous and widespread lesions of blood vessels and to frequent involvement of serous membranes. We then tried to correlate the clinical symptoms with these structural alterations. We maintained that the co-existing endocardial, vascular, serosal and joint involvement must be the manifestation of a primary injury of the endothelial cells and that acute lupus erythematosus could be explained as the result of the action of an endotheliotropic injurious factor. Within the following years similar observations were reported by Jarcho,[11] Denzer and Blumenthal,[12] and Rose and Pillsbury.[13] Ginzler and Fox [14] added lymph node necrosis to the anatomic findings. The report of Rakow and Taylor [15] deserved special mention because it concerned a patient with the characteristic clinical symptoms of acute lupus erythematosus but without any cutaneous manifestations. Characteristic vascular lesions were found within the lungs and kidneys.

Other authors dissented. Some asserted that on the one hand they could not recognize identical lesions in a considerable percentage of their cases, and on the other hand others believed that the histologic alterations reported by us were not characteristic but could be found in other toxic diseases.[16] This criticism called for further study. A series of 12 new cases afforded the opportunity. Microscopic examination revealed not only vascular lesions but other tissue alterations which had not been noticed previously. Restudy of the old material disclosed that identical changes had been present but had eluded our attention. These histologic findings were fully described and illustrated by us in 1941,[17] and a detailed account can therefore be omitted.

Our microscopic observations showed the presence of a widespread alteration of the connective tissue, affecting the heart, serous membranes,

vasculature, lymph nodes, skin and mediastinal and retroperitoneal area. In two recent observations the capsule of the shoulder joint showed identical involvement (figure 1). The morbid process becomes manifest in focal fibrinoid metamorphosis of the collagenous fibers resulting occasionally in fragmentation of these elements, and in swelling and increased density of the interfibrillar homogeneous ground substance which normally is almost invisible. Such foci are more or less heavily infiltrated by polymorphonuclear leukocytes and lymphocytes. The fixed connective tissue cells, fibroblasts and histiocytes, while increased in number, almost invariably show evidence of decay such as pyknosis and nuclear fragmentation. The behavior of the

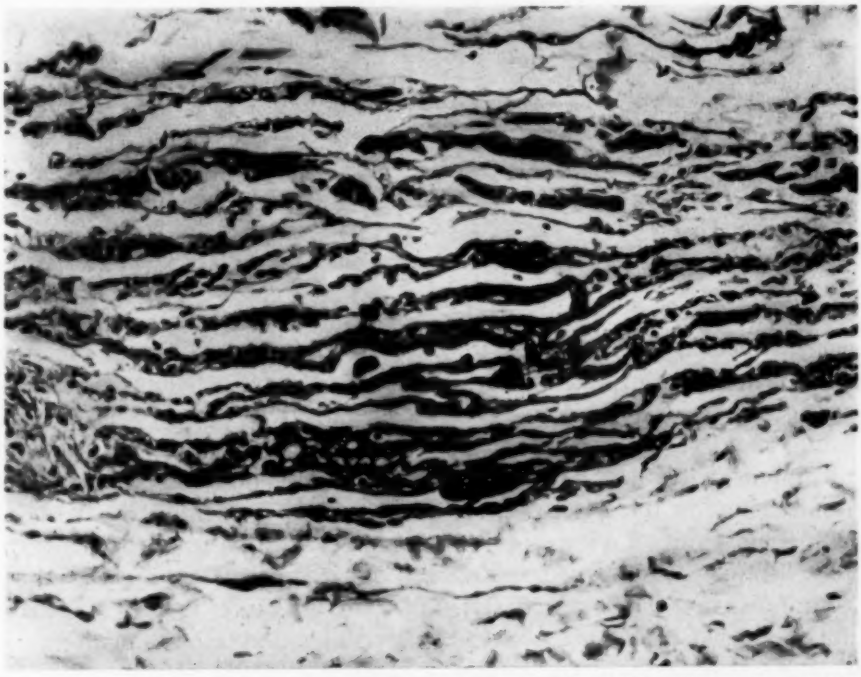

FIG. 1. Capsule of shoulder joint showing thick and eosinophilic collagen fibers, which gave staining reaction like fibrin.

cells in the injured portions of the cardiac connective tissue permits of a differentiation from the injury in rheumatic fever in which fibrinoid alteration is also evident. In rheumatic fever the histiocytes show conspicuous and sustained proliferation, which leads to the formation of the characteristic Aschoff cells. Such cells are absent from the heart in acute lupus erythematosus. The arterial lesions of lupus erythematosus which are predicated upon an injury of the connective tissue framework of the vessel are associated with a mild perivascular cell infiltration. This contrasts with the striking perivascular cell infiltration and proliferation of periarteritis nodosa in which, however, fibrinoid alteration also plays a significant rôle. The alteration of

the glomerular capillaries (wire loops and focal necrosis), so conspicuous in acute lupus erythematosus, has been observed neither in rheumatic fever nor in periarteritis nodosa. Another microscopic feature present with conspicuous frequency in acute lupus erythematosus but not observed in rheumatic fever and periarteritis nodosa is sclerosis of collagen fibers around the follicular arteries of the spleen. This lesion also reflects a fundamental alteration of the connective tissue though of a nature different from fibrinoid metamorphosis. In a review of 20 cases of acute lupus erythematosus we observed the alterations here referred to with such frequency (table 1) that

TABLE I

Collagen Alterations Observed in 20 Consecutive Cases of Acute Lupus Erythematosus

Pericarditis	14 or 70%
7 or 35% showed conspicuous collagen changes	
Heart	
Endocardium	11 or 55%
Myocardium	7 or 35%
Kidney	
"Wire loop" changes	12 or 60%
Focal loop necrosis	17 or 85%
Vascular lesions	8 or 40%
Vessels and other sites	13 or 65%
Spleen	19 or 95%

we felt justified in inferring that they were significant. Because the structural alterations are primarily localized within the extracellular portions of the connective tissue (fibers and ground substance) they cannot be classified according to the conventional principles of cellular pathology, as degenerative or inflammatory. But it is apparent that they are the manifestations of an essential change in the physico-chemical state of these connective tissue elements. This point of view applies, of course, to all the phenomena with which anatomic pathology is concerned. But it is of greater significance for the comprehension of abnormal states of the connective tissues. The association of morbid conditions of cells with visible alterations of structure has been under investigation for nearly a century. These studies have been facilitated by the clear definition of the two constituents of the cells, the nuclei and the cytoplasm. The series of structural alterations which denote an altered state of life of the cell until its ultimate death is well known. In contrast, the intercellular substances, and especially the homogeneous ground substance of the connective tissues, have received much less attention. The microscopic definition of the latter has been made most difficult because conventional methods of histologic preparation render it poorly visible. Therefore, it is reasonable to assume that only certain profound alterations of its physical and chemical constitution become evident upon microscopic examination. This premise is illustrated by the experience that in total scurvy the fundamental disturbance of the intercellular substances is not directly visible. It seems, therefore, not too speculative to believe that significant

alterations of the intercellular substances may exist in other maladies although they cannot be recognized with the available histologic methods. This hypothesis may explain the absence of striking microscopic lesions in some of the cases of acute lupus erythematosus. It also should stimulate investigations with other methods than those of conventional histologic technic, attention being paid especially to alterations of the connective tissue which might easily be neglected because of their apparently trivial character. In two recent cases I was impressed by a striking widening of the myocardial septa which could have been interpreted as mere edema (figure 2A). However, the application of mucus stains (toluidine blue) revealed intense metachromasia, which indicated the conspicuous presence of mucoproteins within the intercellular ground substance. This was associated with only a minimal fibrinoid alteration of the collagen fibers (figure 2B). I believe that the present state of information permits us to conclude that acute lupus erythematosus is defined anatomically as a disease characterized by a fundamental alteration of the collagenous portions of the connective tissue. The exact nature of this alteration must be determined by investigation with the methods of histology, biochemistry and biophysics.

Generalized scleroderma, like acute lupus erythematosus, was originally regarded as a primary cutaneous disease. Histologic examination revealed a conspicuous thickening and homogenization of the connective tissue of the corium. Similar sclerosis was soon observed within the vessels of the skin and in those of the internal organs. Subsequent pathologic investigation disclosed a sclerotic involvement of the alimentary tract, lungs, heart and skeletal muscle. This sclerotic process can be traced to the connective tissue framework of these organs and appears to be the result of an increase in fiber formation. This may or may not be accompanied by proliferation of fibroblasts. In association with this progressive sclerotic transformation of the collagenous elements, fibrinoid alterations were observed by several authors (Masugi and Ya-Shu,[18] Pollack,[19] Bevans[20]). The lesions showed some similarity with those occurring in acute lupus erythematosus. Since sclerosing collagen alterations occur in the spleen of acute lupus erythematosus it may be inferred that fibrinoid metamorphosis and sclerosis represent different phases of a disturbed chemico-physical state of the collagenous tissue. Certainly the morphologic evidence permits the conclusion that generalized scleroderma is likewise characterized anatomically by a fundamental implication of collagenous tissues.

The observations previously summarized indicate that acute lupus erythematosus shares a common element with generalized scleroderma, rheumatic fever, and even periarteritis nodosa in the systemic involvement of the collagenous tissue. This similarity might be interpreted as implying that all these diseases are closely related pathogenetically. In my opinion such an inference is unwarranted.

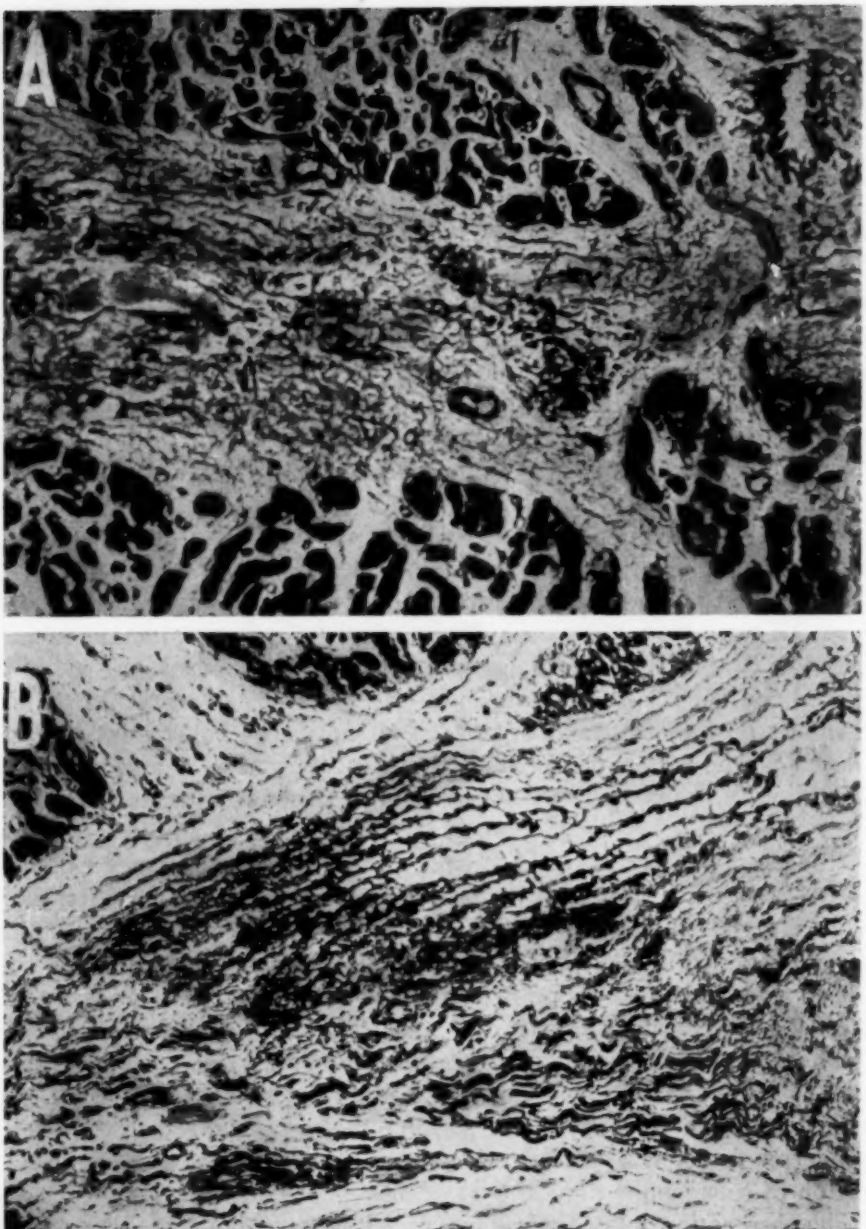

FIG. 2A (*above*). Myocardium showing widened septa with conspicuous interfibrillar ground substance which showed metachromasia with toluidine blue; this is indicative of the presence of mucoproteins.

FIG. 2B (*below*). Same case. Myocardial septum showing fibrinoid alteration of collagen fibers.

Structural alterations are the manifestations of a reaction to injury. Since the modes of reaction of which a tissue is capable are not unlimited, different injuries may provoke similar responses. The question, then, arises what conclusions, if any, can be drawn from morphologic investigations as to the etiology of acute lupus erythematosus.

Painstaking bacteriologic examinations during the life of the patients and of the tissues after death have failed to disclose bacteria as the immediate cause of the disease. Yet the acute or subacute febrile course and the severe toxic symptoms still suggested an infectious process. Hypersensitivity to bacteria or bacterial products was, therefore, proposed as a probable cause (Stokes [21]). This hypothesis is strengthened by the fact that fibrinoid collagen changes have been found as a conspicuous feature of the morbid anatomy of acute lupus erythematosus (Fox,[22] Theilum [23]). The occurrence of similar changes in generalized scleroderma has persuaded Masugi and Ya-Shu to assume that this disease is likewise of allergic origin. It is generally accepted that fibrinoid collagen alterations occur in allergy. This was first demonstrated by Gerlach [24] and Klinge [25] in animal experiments. Its occurrence in diseases with an obvious allergic background such as periarteritis nodosa (Gruber [26]) and serum sickness (Clark and Kaplan [27]), and in drug hypersensitivity (Rich [28, 29]) supply further evidence for a pathogenetic relationship. The allergic hypothesis of the etiology of rheumatic fever, while not yet fully proved, certainly deserves serious consideration. Yet we must not lose sight of the fact that collagen alterations hardly distinguishable microscopically from those seen in allergy can be observed in situations which bear no relation to hypersensitivity. It has long been known that fibrinoid collagen alterations occur in a variety of acute bacterial infections; this fact has been stressed even by Schosnig,[30] a student of Klinge, the most ardent advocate of the significance of collagen alterations in allergy. Identical changes can be observed in inflammations due to chemical or physical irritation (figure 3A). In experimental hypertension, conspicuous vascular lesions simulating periarteritis nodosa have been reported repeatedly (figure 3B). The alteration which is so often found in collagen fibers in the base of a peptic ulcer or in the vicinity of acute pancreatic necrosis is strikingly similar to fibrinoid collagen changes. Finally Wu Tsai Tong [31] showed that simple squeezing of the skin of rats results in collagen alterations indistinguishable from fibrinoid changes. Routine material received in the laboratory of surgical pathology, especially needle biopsies, frequently shows the effect of such undue compression. These observations seem to justify the general conclusion that fibrinoid collagen alteration must not be interpreted solely and invariably as an expression of hypersensitivity. Consequently, I hesitate to accept the doctrine that any disease anatomically characterized by such connective tissue lesions is presumably of allergic origin. Obviously, if observations during the life of the patient so clearly reveal allergic manifestations as in serum sickness and periarteritis nodosa stubborn

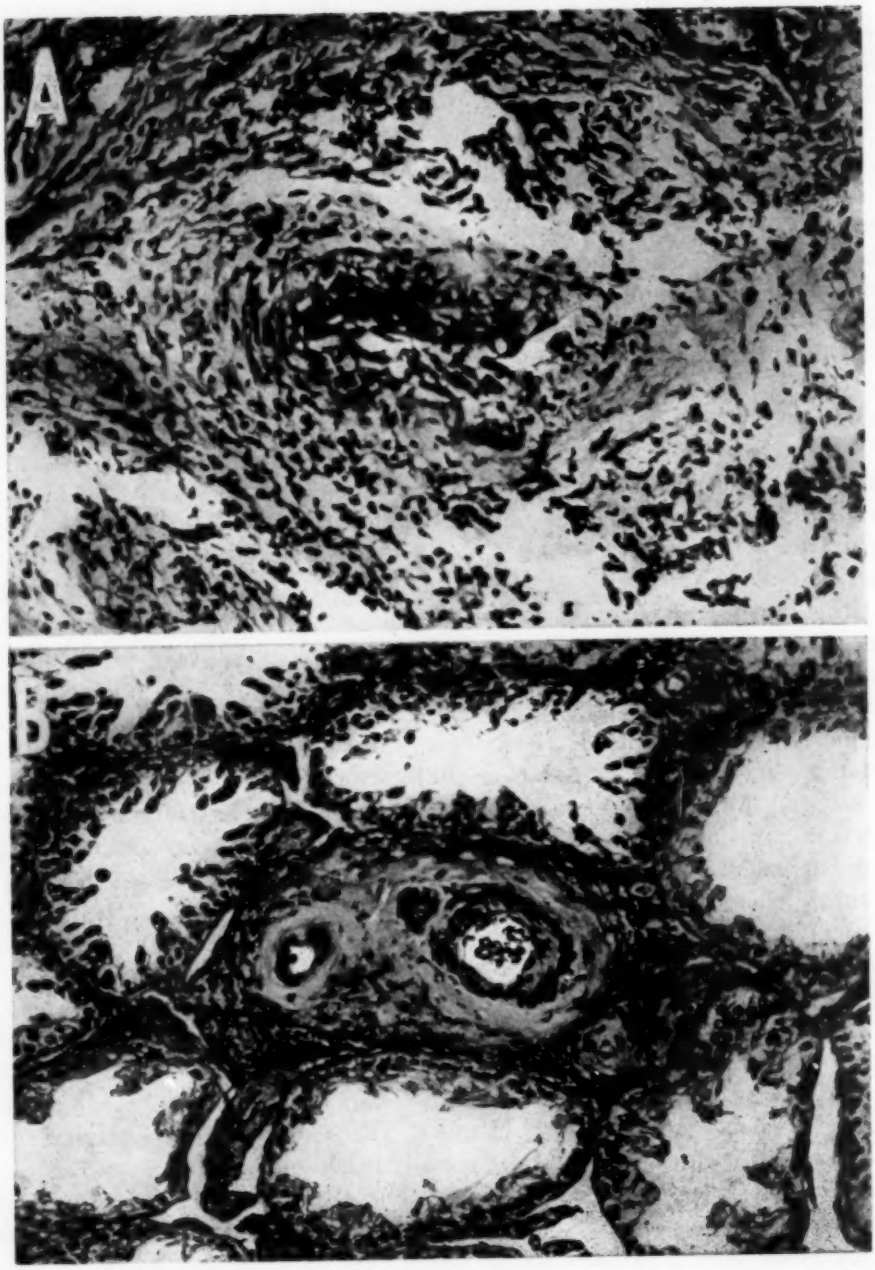

FIG. 3A (*above*). A small artery in the base of a cutaneous ulceration due to roentgen-ray burn showing segmental fibrinoid alteration with necrosis.

FIG. 3B (*below*). Testis of rat with experimentally produced hypertension showing small arterioles with fibrinoid alteration of the wall.

skepticism would be unsound. But there is no direct clinical evidence in support of hypersensitivity in acute lupus erythematosus and in generalized scleroderma (Baehr and Pollack [32]). An allergic hypothesis rests, therefore, upon the histologic features alone and it must be stressed that these anatomic facts have not yet been analyzed sufficiently to permit of a final pathogenetic synthesis.

At this juncture it may well be asked whether and in what way further studies in anatomical pathology can contribute to a clarification of the pathogenesis of acute lupus erythematosus and allied conditions.

The mere perception and description of structural alterations can no longer be the ultimate aim of anatomic investigation. Effort must be directed toward a comprehension of the chemical and physical state which is responsible for the altered microscopic appearance. This aim of anatomic pathology in general is still far distant.

The morbid process of acute lupus erythematosus and scleroderma affects the collagenous tissue system of the body in a conspicuous manner, but we cannot comprehend its nature, because even the normal structure of this matrix is still incompletely understood. Examination of the connective tissue fibers with the aid of the electron microscope and roentgen-ray diffraction have disclosed their molecular structure (Schmitt [33]); but very little is known of altered collagen fibers. In particular, the fibrinoid metamorphosis which is so conspicuous in acute lupus erythematosus and allied conditions requires more adequate definition. It has not yet been ascertained whether the peculiar appearance of the collagen fiber is due to a material alteration or merely to impregnation with true fibrin or possibly the result of a combination of both factors. Attention has already been called to the fact that fibrinoid collagen changes occur in various unrelated conditions. The conventional methods of histopathology can not establish with certainty that the microscopic similarity reflects an actual identity of the chemical and physical constitution of the affected fibers.

Microscopic evidence points to an alteration of the homogeneous ground substance as a significant feature of the morbid process in acute lupus erythematosus and generalized scleroderma. But the nature of the homogeneous ground substance, its relation to the fibroblasts and to the connective tissue fibers still awaits fuller comprehension. Old and recent observations indicate that the ground substance is composed of a variety of mucoproteins. It is known that its colloidal state is affected by enzymes, such as hyaluronidase (K. Meyer [34]). Various female sex hormones seem to exert an opposite influence (Sprunt et al.[35]). By repeated injections of estrogen Leo Loeb and associates [36] produced hyaline changes in the stroma of various organs, while Selye [37] provoked strikingly mucinous edema of the skin in hairless mice by the repeated application of estradiol. The influence of ascorbic acid upon the ground substance and its relation to collagen fiber formation has been ascertained by Wolbach and Howe [38] and Wolbach.[39] Such fragmentary

observations must be expanded and united. By purposeful experimental studies we must try to identify structural alterations of the connective tissue in terms of reactions to well defined chemical and physical influences. Only upon such basic investigations can a successful inquiry be established into the cause of such puzzling diseases as acute lupus erythematosus, generalized scleroderma and allied conditions.

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THE CARDIAC LESIONS OF ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS *

By ELEANOR M. HUMPHREYS, *Chicago, Illinois*

ACUTE disseminated lupus erythematosus is a disease of unknown etiology and of polyphasic symptomatology which quite frequently affects the heart. Views are conflicting as to its true nature, and as to the pathogenesis of its focal lesions. Despite the polymorphism of its lesions, it is possible to recognize certain common and even highly characteristic features, clinical and pathological. It may at first seem unreasonable to group for analysis cases with and cases without the typical cutaneous eruption of acute lupus erythematosus. Although we have long been used to thinking of rheumatic fever without rheumatic joints, we are only now learning that other members of this group of diseases which affect the connective tissues, lupus erythematosus, dermatomyositis and scleroderma, may exist without their classical dermatologic manifestations.

From many studies of cases of acute systemic lupus erythematosus it is clear that there is great variability in the early symptoms and that arthritis, pleuritis and other less well defined complaints may long precede the appearance of the typical erythemas. The group of 21 cases forming the basis for this report includes 15 patients who had, while under observation, lesions considered to be typical. Four others described eruptions which were at least suggestive, and in two patients there was no story of cutaneous involvement. The group shows the usual predominance of females, with 17 between 19 and 39 years of age and two above 50. Of the older females, one, aged 52 years, had a typical facial eruption, as well as pathognomonic endocardial lesions. The oldest patient, a woman of 55 years, had some atypical symptoms but her acute generalized eruption was identified clinically and by biopsy as acute lupus erythematosus. Each of the two men in the group was 52 years old—a somewhat higher age than in most of the reported cases among males. One had a typical facial "butterfly" as well as erythematous patches on the extremities. The clinical course was brief, ending with pneumonic complications. The other male had no recognizable cutaneous eruption, but a classical endocarditis of the Libman-Sacks type found at autopsy was considered adequate to establish the diagnosis.

All 21 patients at one time or another had complained of malaise and weakness, of pains in the joints and muscles, of pleurisy, and of vague abdominal distress. Anemia, and leukopenia (except at times of infectious complications) were invariably present. The same was true of tachycardia. At some period every patient had pulse rates above 100 per minute. Rates between 120 and 140 were noted frequently, and values of 160 to 180 were

* Received for publication May 26, 1947.
From the University of Chicago, Chicago, Illinois.

noted occasionally. Symptoms of local vasomotor disturbances were sometimes conspicuous. Some patients complained of retrosternal distress. Others had severe upper abdominal pains with nausea and vomiting. In the late stages the course was often dominated by the signs and symptoms of failing renal function associated with glomerulonephritis; of diffuse or focalized cerebral disease; of pulmonary disease. Obviously with the preterminal development of decubitus ulcers, of abscesses, of buccal or esophageal or intestinal erosions, bacterial infections frequently complicated the final stages. It is highly probable, too, that therapeutic measures sometimes modified the terminal course, and the character of lesions. One other group of clinical manifestations must be taken into account in any analysis of cardiac status. These are the effects of general debility, often verging on cachexia. These patients frequently suffered from severe anorexia, and many of them lost 20 to 30 per cent of their body weight. The low plasma albumins and low A/G ratios of most of these patients should be noted, as well as the increased globulin levels. Apparently false-positive Wassermann or Kahn tests were observed in at least 10 of the 21 cases.

It is not necessary to discuss in detail the characteristic valvular and mural non-bacterial vegetations, first reported by Libman and Sacks [1] and since described and pictured by many others.[2, 3, 4] It might be well to stress that they may be far from obvious, if they are flat spreading lesions on valve surfaces, or if they are hidden away, beneath the cusps, or in the deeper niches between muscular trabeculae. They may be found on any of the four valves, or in any chamber. Endocardial lesions were found in 12 of our 21 cases, and were hard to detect in four hearts in which they had become almost completely organized. Save for the bulkier lesions affecting two, three, or four valves (observed in seven cases) endocardial lesions were easier to recognize in microscopic sections than they were grossly.

Some focal myocarditis was encountered in most of the 21 cases. At the mildest the lesions were indistinguishable from the minor scarring of rheumatic or arteriosclerotic disease, or were indeterminate small exudative lesions of doubtful significance. Obviously these may have been unrelated to the major disease. More significant were the fine scars, like those of small infarcts; the increased density of collagen along many or most of the intermuscular septa; the thickened small arteries. Myocardial lesions of these types, probably due in part to anoxia were found beneath the more extensive mural vegetations, or near partially or completely occluded arteries. Also there were acute exudative reactions, not easily interpreted. Fresh fibrinoid necrosis of collagen or of vessel walls was easily demonstrable in the more severe cases. In a considerable number of hearts, there was marked loosening of the fibrous substances, producing an edematous appearance not unlike that of the beri-beri heart. In several, severe fatty degeneration of myocardial fibers was noted. No active rheumatic lesions were seen.

In a number of patients, there were no changes other than interstitial edema, atrophy of fatty tissue, and the presence of dense collagen and a few

round cells near the epicardial surface. More often there was a frank pericarditis, affecting visceral and parietal pericardium and the adjacent pleura and mediastinum. In nine cases the process was serofibrinous, and in five of these (all with nephritis) there were effusions of 600 to 950 c.c. In six cases the pleural space was obliterated by loose gelatinous fibrous adhesions. There were foci of fresh necrosis, or of fibrinous and cellular exudation, within these adhesions.

The presence of adhesions or shaggy exudates as well as the edema and scarring of the walls interfered with precise estimates of cardiac weight. In proportion to the wasted state of the bodies of these patients, the cardiac weights were usually normal or increased (est. 250 to 300 gm.). In the patients who had nephritis for a sufficient period, weights of 350 to 450 gm. were observed. The larger hearts were found in patients whose nephritic symptoms had been present long enough for hypertension to develop. In one such patient the blood pressure had risen from 115 mm. Hg systolic and 75 mm. diastolic to 170/120 as the disease progressed. The blood pressures were usually normal or more often low, in the absence of renal disease.

Electrocardiographic data were available for 17 patients, with from one to three tracings per patient. While the examinations were not always made at periods of severe symptoms, there was, in general, a fair correlation with the severity of myocardial lesions. The commonest finding was lowered amplitude with evidence of minor myocardial abnormality. Arrhythmias, with extrasystoles, were observed three times. In one other case the tracing demonstrated an auricular flutter with a 2 : 1 ratio and a ventricular rate of 175 per minute. This tracing was made two days ante-mortem, on a young woman with severe myocardial and endocardial disease.

In conclusion, it is obvious that it is often impossible to evaluate with any precision the severity of the cardiac lesions in the patient with acute lupus erythematosus. The patient dying of this disease often presents simultaneously, symptoms related to a polyserositis, including a pericarditis; to acute or chronic renal disease; to abnormalities of the nervous system; to nutritional disturbances; to chronic and acute pulmonary disease; to acute bacterial infections. At least a few of them have had preceding rheumatic heart disease. It is obvious why so little precise information can be obtained, with the technics of physical diagnosis. Probably the best clue to the severity of cardiac injury is a series of electrocardiograms. Even this tool is subject to confusion, particularly in the presence of a pericardial effusion.

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THE PHYSICAL EXAMINATION: HELPS AND HINDRANCES *

By JAMES J. WARING, M.D., F.A.C.P., *Denver, Colorado*

"But it is by your own eyes, and your own ears and your own minds and (I may add) your own heart that you must observe and learn and profit." A. Latham. Harvey Cushing "The Life of Sir William Osler," Clarendon Press, 1925, p. 553.

THE five essentials to a good physical examination are:

1. A good light
2. A favorable position of the patient
3. A quiet environment
4. A coöperative patient
5. An experienced physician.

Without any or all of the first four even the experienced physician is under a handicap. The physician must not let the patient for his own sake even unconsciously impose conditions of the examination which may seriously interfere with the effort to obtain information necessary for diagnosis and treatment.

1. A Good Light. Because he had the rare faculty for imparting information in a memorable fashion, William Osler was a great teacher. He used with equal skill admonition, sarcasm, humor, classical allusion and even the device of stage-setting. On the occasion of a visit by Dr. Alexander Lambert of New York to the wards of the Johns Hopkins Hospital, Osler unobtrusively manoeuvered Dr. Lambert into a position between the window and the patient's bed. The stage thus set, he asked the student to present the case.

Osler: "How will you begin the examination of this patient?"

Student: "I will begin by inspecting him."

Osler: "No, Sir: Not yet. Something before that."

Student is at a complete loss.

Osler: (*putting his arm around Dr. Alexander Lambert's shoulders and pointedly drawing him out of the light*) "You would first say 'Alexander, please stand out of my light.'"

Thereupon would follow a rapid interrogation, often only by glance of those piercing eyes, to see which ones knew the ancient story of Diogenes,

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The illustrations in this paper were made at my direction by Allen T. True of Denver. The medical profession has perhaps limited itself too much to photographic illustration. A point humorously depicted might linger longer in the memory.

the Cynic Philosopher who lived in a tub, and Alexander the Great (figure 1).

"What can I do for you," said Alexander.
"Just stand out my light," replied Diogenes.

So runs the story. Today Diogenes would promptly reply: "Please find me an apartment, Alex! This tub has no facilities."

I believe this story has great teaching value and use it occasionally on the wards of the Colorado General Hospital to fix in the students' minds the

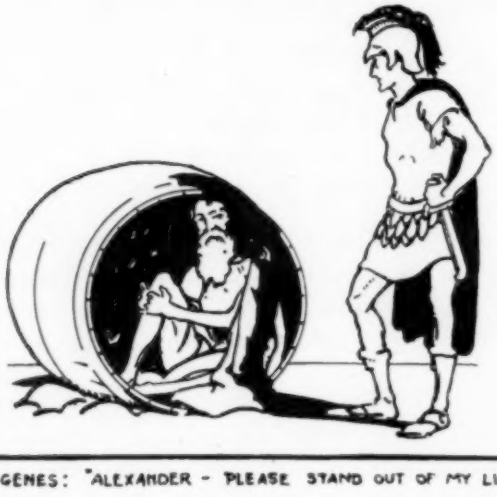

FIG. 1. The first essential to a good physical examination is to have the patient in a good light.

importance of a good light for a good examination. Practical illustrations could be multiplied.

Take just one:

For a week a student nurse had suffered from nausea, vomiting, general abdominal distress and fever. Except for a slightly tender right hypochondrium the physical examination was said to be inconsequential, the white blood count and the urinalysis were normal. The resident staff was puzzled.

I found the patient in a four bed room in a cubicle farthest removed from the window.

"Pull the bed over by the window so we can have a good look at her," was my first order. It was done.

"Why," said the surprised patient to the equally surprised staff, "I'm jaundiced!"

2. A Favorable Position of the Patient. I have chosen a fat Dowager (figure 2) in the middle of a huge low bed to illustrate my next point: the patient must be in a position to facilitate not obstruct the examination. All parts of the patient's body must be easily accessible to the examiner's hand and eye. This poor lady has to have a low bed because she is too heavy and unwieldy to get into a high one. A narrow bed would be dangerous because she would siphon off on to the floor if her panniculus ever started overflowing the edge of the bed. So there she lies and your problem is to find out what ails her *without breaking your back.*

Now, to get the patient in a favorable position for examination may involve nothing more than having the disrobed patient sit up or lie down. In

FIG. 2. The patient must be in a position to facilitate not obstruct the examination.

the case of our Dowager, there she sits in a dim light, insulated by adipose tissue, bed clothes and distance, a lardaceous atoll in a Pacific ocean of feather bed, while you circle helplessly, so to speak, three miles off-shore, wondering what the hell is going on inside the old gal!

What to do? Get the best light in the room you can; daylight is always preferable to artificial light. While someone gets the gown off and a wrapper on you consult the bath-room and run some hot water on your cold hands and the cold bell of your stethoscope!

You now go over your patient in bed systematically from head to feet, not neglecting the neurological examination and a careful appraisal of the state of the circulation in the lower extremities. Then, even though it may take

much effort, a derrick and half the neighborhood,* you get the patient out of bed and in a straight chair in a good light for further and more satisfactory examination of heart and lungs. The distortions of physical signs produced by asymmetrical positions in bed sometimes defy reliable separation from the signs of disease. A position of the body, therefore, favorable for a good examination involves first, accessibility to the examiner and secondly, symmetrical arrangement of trunk and extremities so that the two sides of the chest may be compared in all particulars.

Examination of the chest with the patient lying on the side in bed is particularly treacherous for at least four reasons: (1) The diaphragm changes asymmetrically level and amplitude of swing, (2) the curvature of the spine changes the costal relations, (3) the air in the mattress acts as a resonator to alter percussion notes, especially over the lung next the bed, (4) hypostatic moisture may be confused with the râles of a basal pneumonia.

While the patient is upright in the chair, do not fail to listen to her lungs beneath her breasts which she can lift out of your way first on one side and then on the other. Basal tuberculosis is rare but occurs often enough even in elderly people.

Among petty grievances of the examining physician I give first place to the lady of some 40 summers who keeps a determined clutch to her nightgown over her not too-curvaceous bosom as you patiently struggle to get an unobstructed "listen" to her heart and lungs.

The average woman submits with reasonable cheerfulness to exposure of her abdomen from the rib margins to the umbilicus. Below this, trespass at your peril! The stubborn clutch of the over-modest woman to the bed clothes as you push them down to the decent "symphysis-pubical" level is another annoyance. You push the covers down, she pulls them up. You somewhat fretfully push them down again and again she pulls them up. Victory in this little contest must rest with the doctor!

Arrange the bed covers yourself and, if need be, summarily dispense with the officious nurse or relative who seems to think that her mission in life is to protect the patient against indecent exposure. Every act of this miserable creature seems a pointed reminder to the physician not to let his thoughts stray from the professional job off into amorous avenues! I suspect this person annoys the patient as much as the doctor. Fortunately, their number is not great.

3. A Quiet Environment. A quiet environment is best obtained by prompt ejection of cats, dogs, canary birds, children and surplus relatives (figure 3). On occasion, a single member of the household may remain to supply information which for one reason or another the patient cannot give.

Suppress firmly but politely all unnecessary talking in the sick-room, whether by family, nurse, patient or colleague.

* The neighbors are always glad to help. It gives them a chance to satisfy their curiosity about our Dowager and an opportunity to meet the Doctor.

Tactfully reassure your nervous colleague who has called you in consultation. The poor fellow is so afraid you will discover something he has overlooked that he gets in your way at the bedside. His head bumps yours, as he tries to look down the patient's throat while you are looking, his hands tangle with yours on the patient's belly, his stethoscope competes with yours for a place on the patient's chest. Don't be this chap yourself and don't let your colleague get that way. Much of your success as a consultant will depend upon your skill in putting at ease early and promptly both the patient and your colleague.

One other piece of advice I consider of great importance to the family physician. Never fail to reëxamine the patient again immediately before the consultant. You thus protect yourself against changes which may have taken place since your last examination. The old alibi "that is something

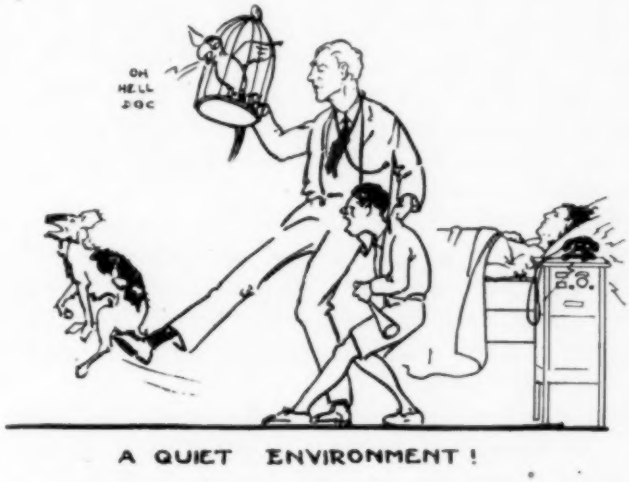

FIG. 3. A quiet environment is best obtained by prompt ejection of cats, dogs, canary birds and surplus relatives.

new" is weak! It carries no conviction to consultant, patient or watchful family.

Too often the doctor, fearful of giving offense, permits conversation in the sick-room between colleague, nurse and relatives and so impairs his examination. In teaching this point about a quiet environment, I tell the boys the story of old Dr. John Abernethy (1764–1831), a somewhat cantankerous English surgeon of great distinction as a teacher. Annoyed by the stream of chatter from the mother of a young woman he was trying to examine, he suddenly said:

"Madam! Stick out your tongue!"
Madam X (*protesting*): "But, Doctor, there's nothing wrong with me."
Dr. Abernethy (*savagely*): "Madam! Stick your tongue out."

Madam X (*red-faced, sticks her tongue out*).
Dr. Abernethy: "Now, Madam! Keep it out." (*He turns back to his examination.*)

One may legitimately assume that Madam X was thereafter *speechless,* with indignation!

In summary, while the doctor makes his examination, every distracting influence must be removed. By tact, diplomacy and force of his personality the doctor must dominate the sick-room.

4. A Coöperative Patient. A coöperative patient may be defined as one who submits willingly if not cheerfully to the examination, who endures real discomfort and all necessary exposures with patience and dignity, who is neither a shrinking "sissy" nor a too-impassive stoic, who responds with brevity and intelligence to interrogation, who volunteers little but enough, who knows the difference between the relevant and the irrelevant. A co-operative patient seems to know instinctively what to do and to say to help the doctor and herself and not to hinder him and herself in his examination. A coöperative spirit is in-born but can be inculcated. Some unfortunates who have seen much illness and perhaps suffered much at the hands of many doctors learn the technic of the examination and make "good patients," others never learn to submit gracefully.

But a satisfactory physical examination does not depend solely upon the patient. Two human beings are involved, the doctor and the patient. The doctor can take a shy, sick woman through a searching examination without either causing pain or wounding her pride. On the other hand, at the very outset, he can demoralize a readily coöperative patient by needless roughness and disregard of finer sensibilities.

The physical examination must be made tactfully, patiently, unhurriedly, thoroughly. Conducted in those terms, it goes a long way toward inspiring confidence and uncovering the cause of the patient's illness.

5. An Experienced Physician. Until now I have spoken in general terms of the physical examination. From here on, I shall speak of specific methods of examination, of the signs and symptoms of disease and their interpretation.

My colleague, Harry H. Gordon, Professor of Pediatrics at the University of Colorado School of Medicine, in a personal communication, points out that errors in pediatric physical diagnosis are easily made through failure to distinguish between negative findings and the results of an incomplete examination. For example, he says, one should distinguish between:

1. Normal discs and retinae and a fundus not seen because of crying, ocular movement or constricted pupils.
2. A normal ear-drum and one not seen because of the use of too large an ear speculum or because of obstruction of the auditory canal by wax.
3. A normal pharynx and one not seen because of regurgitated milk.
4. Normal auscultatory findings and ones obscured by the child's crying.

5. Normal abdominal findings and ones obscured by involuntary abdominal rigidity due to crying.

The importance of being sure that you have had an adequate "look," a satisfactory "feel" and an undisturbed "listen" is just as fundamental to good physical diagnosis in the adult as in the child.

Gordon also called my attention to a very practical point in the diagnosis of meningitis in an infant. The tension of the patent anterior fontanelle is a good measure of intracranial pressure and is thus of considerable aid in diagnosis. If the infant with meningitis is badly dehydrated or in circulatory collapse, the pressure of the cerebrospinal fluid will be low instead of high and the fontanelle depressed instead of bulging. After hydration or correction of the circulatory collapse, the increase in tension of the fontanelle will become apparent.

Examination of the Chest. The experienced physician knows that minimal tuberculosis is not detectable by the stethoscope and that for early diagnosis he must depend upon the timely chest film. He also knows that in examining the chest he must listen carefully for râles during the inspiration following a forced expiration and repeated cough. This procedure long known to chest specialists and taught in every school in the land is too frequently neglected in practice. The limitations of each method of examination must be learned. To master physical diagnosis of the chest, it is only necessary to have good eyes, good ears, one stethoscope,* a fluoroscope, a good roentgenographic unit, a ration of intelligence, a measure of determination and a mess of patients. Thereafter stethoscope in hand one moves repeatedly back and forth, back and forth between the patient and the film until the film can be faced without fear of surprising and therefore unpleasant revelations. *The roentgen-ray should be used not merely for diagnosis but as a teacher of physical diagnosis.*

Wheezing due to bronchial asthma is of long standing and is generally distributed. A localized wheeze of recent development is strongly suggestive of bronchial obstruction. This type of wheeze may also be heard with the bell of the stethoscope held about three inches in front of the open mouth of the patient (figure 4). The most common causes are bronchial tuberculosis, bronchial adenoma, endobronchial carcinoma, foreign body in the bronchus. Chevalier Jackson's dictum is worth remembering: "All is not asthma that wheezes."

In recent years one of the great advances in the diagnosis of diseases of the chest has been increasing recognition of collapse of part of a lung and its causes. For the final solution of these pulmonary problems, fluoroscopy, roentgenography, bronchoscopy and bronchography are indispensable. However, in routine physical examinations certain observations may be made quite easily to determine whether all parts of the lungs are well ventilated.

Does the chest expand equally on the two sides?

* Kerr's symballophone is a very useful instrument for the analysis of murmurs.

FIG. 4. Jackson's dictum is worth remembering: "All is not asthma that wheezes."

Is the trachea in the mid-line?

Where is the point of maximum apical impulse?

Do the two halves of the diaphragm move equally and what are their levels?

That movement of one side of the chest may be restricted in pneumonia, pleurisy with or without effusion, simple or complicated pneumothorax, old pulmonary tuberculosis is well known. To these should be added bronchial obstruction and the subsequent atelectasis of part or all of one lung.

The position of the trachea can be determined best by Gerald Webb's technic (figure 5). The examiner places the thumb of his right hand on the

FIG. 5. In this test, the palpating "finger" is the thumb.

right side of the patient's neck between the larynx and the sterno-cleido-mastoid muscle and by gentle pressure on the thyroid cartilage determines its position and mobility much as in the vaginal examination the position and mobility of the cervix are determined. Then, the examiner swaps hands and places the thumb of his left hand in a corresponding place on the left side of the patient's neck between the larynx and the other sterno-cleido-mastoid muscle and again by gentle pressure toward the mid-line determines the position and mobility of the larynx and so the position of the trachea. The Holmes-Sellors test with a finger in the suprasternal notch is similar.

The significance of a Horner syndrome and unilateral or bilateral clubbing of the fingers will not be over-looked.

Is it part of the physical examination to look in the patient's sputum cup to see what sort of stuff is being raised? I think so! Most important information can be secured from simple naked-eye inspection of sputum and, it should be added too, by smelling it! (figure 6). The odor, appearance and

FIG. 6. The odor, appearance and the quantity of the sputum and their variations carry diagnostic and prognostic implications.

the quantity of the sputum and their variations carry diagnostic and prognostic implications. I have often said that I could tell with a fair degree of accuracy how the patients in a tuberculosis sanatorium were getting along by simple day after day inspection of their sputum cups.

The physician must not only have an inquiring mind, he must *cultivate* an inquiring mind. He must constantly ask himself why the patient has a rash, why he has a sore throat, why he has fever or what-not? Why does the patient have a "water-hammer pulse"? Does he have aortic regurgitation, patent ductus arteriosus, or coarctation of the aorta? To stimulate the student to exercise the inquisitive part of his brain I have built a lesson

around the phrase I just used—"the water-hammer pulse." A diagnosis of aortic regurgitation having been made, my inquiring mind subjects the inquiring mind of the student to the following inquisition:

"Why do you think this patient has aortic regurgitation?"
Answer: "Well, in the first place, he has a water-hammer pulse."
"Yes! He has a water-hammer pulse! By the way, what is a 'water-hammer'?"

Silence

There follows instruction to look up the meaning of the term "water-hammer," instruction how to make a "water-hammer" and finally orders to demonstrate the newly made water-hammer to the class at the next meeting. One is easily made with a test-tube, a little water and a bunsen-burner.

All this to the end that the student will be impressed with the thought that he must learn and practice the habit of inquiry.

The experienced physician will not miss a pulsus alternans with his finger on the radial artery but he will know how to check this observation with the sphygmomanometer. He will be familiar with normal and abnormal venous pulsations in the neck and will not confuse them with carotid arterial pulsations. He will not miss a pulsating liver and will know its significance. He will not miss a thrill because he failed to palpate for it with the patient sitting up, leaning forward with the breath held at the end of an expiration. He will not fail to listen to the heart with the patient lying down, sitting up, before and after exercise, and leaning forward with the breath held at the end of expiration.

Examination of the Abdomen. In examining the abdomen, he will not fail to have the patient point to the location of his pain. The experienced physician will look for liver enlargement in the mid-line as well as below the right costal margin. He will use Middleton's manoeuver and will place the left hand and forearm of the patient under the left lower ribs as he palpates for an enlarged spleen.

He will not fail to make a careful neurological examination (figure 7) or to appraise the circulation in the legs, especially in the elderly patient. He knows that by simply moving the ulnar border of his hand gently over the surface of an extremity up and down foot to hip and back that he can with great accuracy define the limits of good circulation. Thomas Lewis' optimal thermo-tactile surface, the dorsal surface of the first phalanges, is generally most useful to detect surface temperature changes but is not as helpful for the specific purpose mentioned.

Our experienced physician will not miss a coarctation of the aorta because he did not compare the blood pressures in the lower extremities with those in the upper! He knows all about phlebothrombosis and thrombophlebitis and pulmonary embolism. He will measure repeatedly before and after operation the smallest circumference in the legs at the ankles and the largest at the

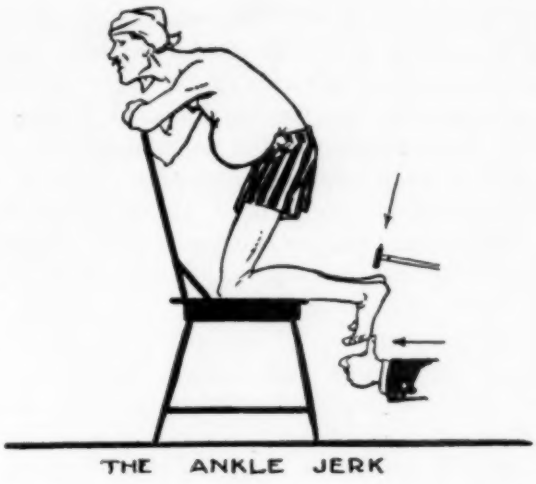

FIG. 7. A useful position for testing the ankle jerks.

calves, and will compare one leg with the other. He will watch for increased firmness or elasticity on compression of the calf, a tendency to resist dorsiflexion of the foot and tender points on the plantar surfaces of the feet. He knows that a thrombosed area in a superficial vein on the back of the calf is, in Homans' words, "a useful proof of deep thrombosis."

The Rectal Examination. Digital examination of the rectum is too often neglected. Hamilton Bailey phrases it unforgettably thus: "If you don't put your finger in it, you will put your foot in it" (figure 8).

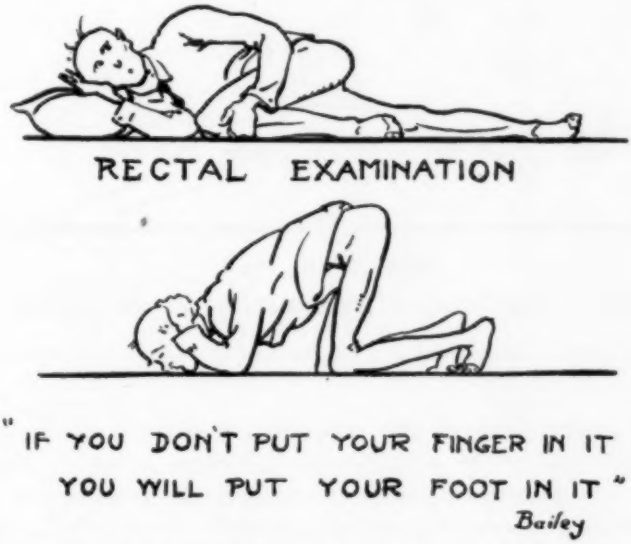

FIG. 8. The digital examination of the rectum is too often omitted.

In children the abdominal examination may be unsatisfactory because the child is fearful it will be hurt. A careful digital examination of the rectum may reveal an acutely tender area on the right side and so establish a diagnosis of acute appendicitis. George Packard, Professor of Surgery at the University of Colorado, tells me that the anal sphincter in a child with generalized peritonitis from a ruptured appendix or in a child with appendiceal abscess has lost its tone and is lax. He considers this a very useful diagnostic sign. The rounded head of intussusception may be felt by digital examination of the rectum and the palpating finger will show the characteristic "currant jelly" smear of blood and mucus.

Approximately 12 per cent of all malignant tumors originate in the anus, rectum or sigmoid. In this region are located 80 per cent of all intestinal cancers, of which 85 per cent are within reach of the finger and diagnosis.

In doing the rectal examination, look for anal fissures, hemorrhoids, polyps, prostatic carcinoma, rectal carcinoma, fecal impaction, a rectal shelf of metastatic cancer. Remember that a fistula-in-ano may be tuberculous and that anesthesia of the anal canal with loss of tone of the internal sphincter and incontinence are characteristics of tabes and taboparesis. It is now quite convenient to remember that testicular insensitivity is a reliable sign of posterior column damage in tabes or taboparesis and you therefore seize the opportunity and the organ to test for it (figure 9). Joseph Earle Moore,

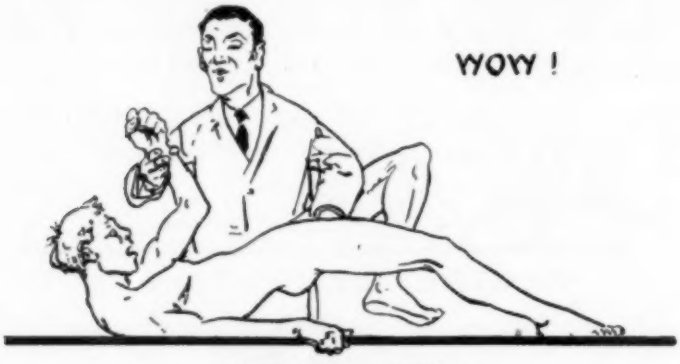

FIG. 9. Testicular insensitivity is a reliable sign of posterior column damage in tabes or taboparesis.

in a personal communication, says insensitivity of the testis "does not occur in any condition except those neurologic disorders in which deep pain sensation is lost. In many tabetics one can squeeze the testis almost to the point of rupture without producing any disagreeable sensations at all." Don't forget that a bimanual examination is useful in the male to discover a cancer

of the sigmoid. Look for tenderness in the pouch of Douglas in suspected ectopic pregnancy and tenderness in the right side of the pelvis in acute appendicitis.

So much by way of specific suggestions as to the physical examination! I would be very remiss if I did not now take you all the way back to the very beginning to emphasize one thing which, doubtless, is as well known to you as all the rest. John lies dead upon his bed. The difference between dead John and dead Richard is perhaps of interest only to the pathologist, but all those things which made the living John different from the living Richard are matters of the greatest concern to all physicians. Time was when these differences were important only to John and Richard and their friends, but of little significance to their family physicians. But, medicine has not stood still. All those things that made the living John different, his strengths and his weaknesses, his hopes and his fears, his joys and his disappointments, his yearnings, all his emotional as well as his organic reactions to his environment, all these things must be weighed by John's physician today, if he would help John! Mind and body have merged into one, the man John, friend, patient! I conclude, therefore, with this statement: The examination begins with the first greeting of the patient by his physician and does not wait the removal of the shirt.

Summary

1. The five essentials to a good physical examination are: (1) a good light; (2) a favorable position of the patient; (3) a quiet environment; (4) a coöperative patient; (5) an experienced physician.

2. The importance of being sure that you have had an adequate "look," a satisfactory "feel" and an undisturbed "listen" is just as fundamental to good physical diagnosis in the adult as in the child.

3. The roentgen-ray should be used not merely for diagnosis but as a teacher of physical diagnosis.

4. Jackson's dictum is worth remembering: "All is not asthma that wheezes."

5. The odor, the appearance, the quantity of the sputum and their variations carry both diagnostic and prognostic implications.

6. The digital examination of the rectum is too often neglected. "If you don't put your finger in it, you will put your foot in it." (Hamilton Bailey.)

7. Finally, the examination begins with the first greeting of the patient by the doctor and does not wait the removal of the shirt.

URINE VOLUME AND TOTAL RENAL SODIUM EXCRETION DURING WATER DIURESIS *

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The value of drastically reducing sodium intake in treating the edema of congestive heart failure is generally accepted. Concerning the optimal water intake during such sodium restriction recommendations have ranged from the older view that fluids should be drastically restricted [1] to the opposite extreme, that fluids should be forced even to five or ten liters daily.[2] While many clinicians [3, 4, 5, 6, 7, 8] favor a middle course and allow moderate or even ad libitum fluid intake, it would seem desirable to know how fluid intake might be adjusted to assure in the average patient the greatest possible excretion of sodium per day. On this important point no extensive studies have been made so far though the relation between chloride excretion and water diuresis has received some attention.[29]

The important questions are (1) does water diuresis uniformly increase total sodium excretion above that observed with moderate urine flow? (2) does water diuresis enhance the sodium excretion produced by the common diuretic drugs? The studies here reported indicate that water diuresis per se increased sodium excretion if urine formation was previously low. If prior urine formation exceeded two to three liters per day water diuresis actually decreased the total excretion of sodium. It appears therefore that a maximal sodium excretion can be obtained in most cases with a moderate urinary volume viz, two to three liters per day. The effects of concomitant water diuresis on the action of diuretics are also considered.

Method. Water diuresis was produced by oral administration of 1,000 c.c. of tap water within 15 minutes. The subject was allowed no food or water after midnight the night before the test. The bladder was emptied at 7:30 a.m. and this specimen discarded. The 7:30 to 8:30 specimen was used as a control. Between 8:30 and 8:45, 1,000 c.c. of tap water were administered orally. Hourly urines were then collected until 1:30 p.m. During the test, the subject reclined quietly in bed except for transient assumption of the erect posture as needed to facilitate voiding.

One to three days later the test was repeated and in addition one of the following diuretic substances was added. (1) Theophylline 0.3 gram at 8:30 a.m. orally. (2) Theobromine calcium salicylate 3.0 grams at 8:30 a.m. orally. (3) Theophylline with ethylene diamine, 0.5 gram intravenously at 8:30 a.m. (4) Urea, 30 grams at 8:30 a.m. orally. (5) Glu-

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cose, 75 c.c. of 50 per cent solution intravenously at 8:30 a.m. and (6) Mercurophylline injection, 2 c.c. intramuscularly at 7:30 a.m. Each substance was tested on a minimum of four patients.

The subjects were about equally divided as to sex and race (white and negro). All adult age groups were included but no patient was above 75 years of age. Urine volume was measured in cubic centimeters. Sodium determination was done with a flame photometer, direct method. The major observation on sodium excretion during water diuresis has been repeatedly checked by a gravimetric determination of sodium [21] and the results of photometric studies confirmed. Approximately 100 observations on water diuresis and sodium excretion have been made on 50 patients.

TABLE I

Urine Volume and Total Renal Sodium Excretion during Water Diuresis in a Patient: (1) with Moderately Severe Congestive Failure; (2) at the Height of Diuresis under Rest and Digitalis and (3) Following Recovery from Failure

	1		2		3	
	Urine Volume c.c.	Total Sodium Mg.	Urine Volume c.c.	Total Sodium Mg.	Urine Volume c.c.	Total Sodium Mg.
5	150	46.7	280	233.4	—	—
4	390	24.8	300	196.0	250	148.5
Hours 3	200	14.6	350	89.9	525	110.2
2	260	143.9	630	169.5	310	89.9
1	100	180.9	290	388.0	260	162.2
Total	1100	410.9	1850	1076.8	1345	510.8

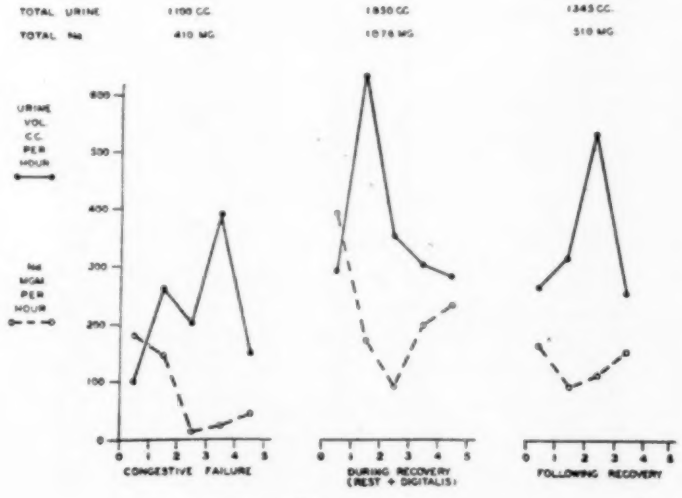

CHART 1.

Water Diuresis and Renal Sodium Excretion. From these experiments, a definite pattern of urine volume and total hourly renal sodium excretion has been recorded over a period of six hours during water diuresis. This pattern is essentially the same in outline for both normal and congestive heart failure patients although a quantitative difference does exist, that is, the urine volume and the total renal sodium excretion during water diuresis varied from high to fairly low values in patients with congestive failure, depending

TABLE II

Patient	Diagnosis	Urine Volume Control Hour	Mg. Na Control Hour	Urine Volume Peak Diuresis Hour	Mg. Na Peak Diuresis Hour
		Group I			
1	Normal	29	48.7	470	40.4
2	Congestive failure	30	49.8	392	25.0
3	Normal	42	74.3	350	60.2
4	Conjunctivitis	58	187.4	460	135.7
5	Coronary insufficiency	72	191.2	310	88.3
6	Neurosis	74	319.3	626	257.8
7	Secondary Lues	82	187.0	512	147.4
8	Neurosis	90	200.0	410	45.0
9	Muscular dystrophy	112	299.6	669	235.4
10	Normal	113	210.1	434	163.6
11	Normal	126	241.0	158	143.7
12	Congestive failure	135	387.0	438	158.5
13	Normal	136	408	750	186.7
14	Neurosis	220	266	550	212.8
15	Normal	222	108.1	534	80.1
16	Neurosis	252	401.9	786	249.5
17	Neurosis	265	268.9	444	176.2
		Group II			
1	Neurosis	10	30.2	275	277.1
2	Congestive failure	11	3.2	102	38.4
3	Normal	14	48	525	156.9
4	Normal	20	56.5	234	119.3
5	Neurosis	27	23.3	478	97.9
6	Normal	29	105.2	710	221.5
7	Neurosis	29	24.9	535	107.5
8	Congestive failure	30	32.8	157	94.9
9	Neurosis	30	110.5	450	154.8
10	Neurosis	31	151.9	785	257.4
11	Neurosis	33	117.1	650	138.4
12	Normal	34	57.1	682	113.2
13	Neurosis	35	166.4	684	305.3
14	Normal	36	126.0	634	181.3
15	Neurosis	38	69.6	670	137.3
16	Normal	38	79.0	494	172.4
17	Neurosis	42	174.9	434	216.5
18	Neurosis	42	104.7	473	160.8
19	Neurosis	49	56.2	838	180.1
20	Hypertension	51	129.5	412	197.7
21	Neurosis	57	178.2	605	248.0
22	Normal	74	109.5	470	131.6
23	Neurosis	99	21.7	518	126.3
24	Congestive failure	113	43.5	468	46.8

on such factors as the amount of edema,[9] the relative state of cardiac competency at the time of the test, the amount of sodium in the diet, and the concentration of sodium in the plasma.[9, 10, 11, 12, 13]

The effect of water diuresis on renal sodium excretion in a patient with hypertensive heart disease and moderately severe congestive heart failure is illustrated in table 1 and chart 1. Water diuresis was observed during: (1) Moderately severe failure (weight 165 pounds and venous pressure 200 mm. of water); (2) At the height of diuresis under rest and digitalis (weight 157 pounds and venous pressure 130 mm. of water); (3) When the patient was edema free and ready for discharge (weight 154 pounds and venous pressure 90 mm. of water). It is apparent that in each instance of water diuresis depression of total renal sodium excretion occurred just as in the normal subjects shown in Group I of table 2. Therefore, many of our experiments have been done on normal people for obvious reasons.

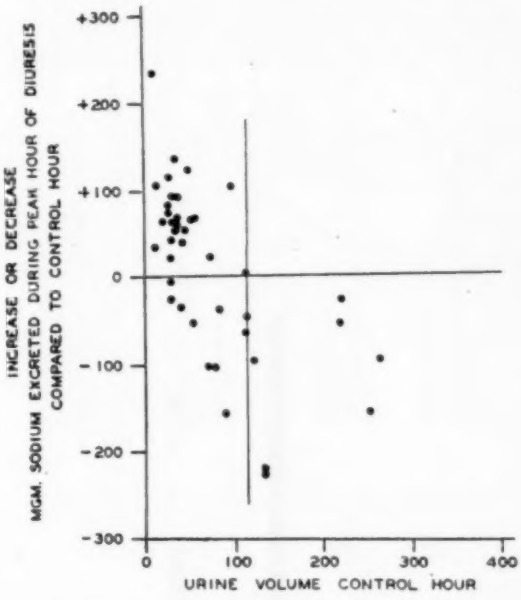

CHART 2.

A comparison is made in table 2 and chart 2 between the total renal sodium excretion during the control hour and during the hour of greatest urine volume. Of the 41 patients, 17 excreted more sodium during the control hour than during the hour of greatest diuresis. The other 24 patients excreted more sodium during the hour of greatest diuresis than during the control hour. The 17 patients will be referred to as Group I and the 24 patients as Group II. The striking difference in the two groups is the urine volume during the control hour with an average figure of 121 c.c. for Group I and 40.8 c.c. for Group II.

Therefore, in Group II urinary flow was below a level theoretically necessary for the adequate excretion of solids[14] while in Group I urinary flow was up to or above adequate flow. Certainly half or more of Group II temporarily did not have enough urinary water during the control hour to excrete sodium and other solids ready for excretion. It seems likely therefore, that the increased sodium excretion at the height of diuresis in this group simply represents the elimination of sodium retained during inadequate urinary flow. Obviously the nature of the experiment does not permit finely adjusted controls and a certain amount of overlap does occur in the two groups. However, it would seem that there is a certain range of urinary volume necessary for the maximal excretion of sodium and above or below this level renal sodium excretion falls off. If adequate urinary flow had been present during the control hour then Group II patients would probably have excreted sodium during water diuresis as did the Group I patients. This problem may be approached in a slightly different fashion.

Total renal sodium excretion in 41 patients for the two hours of greatest urine volume and the two hours of smallest urine volume is shown in table 3.

TABLE III

Average urine volume and total renal sodium excretion during water diuresis in 41 patients for the two hours of smallest urine volume and the two hours of greatest urine volume

Smallest	Greatest
257.4 c.c.	799.4 c.c.
336.0 mg. Na	330.8 mg. Na

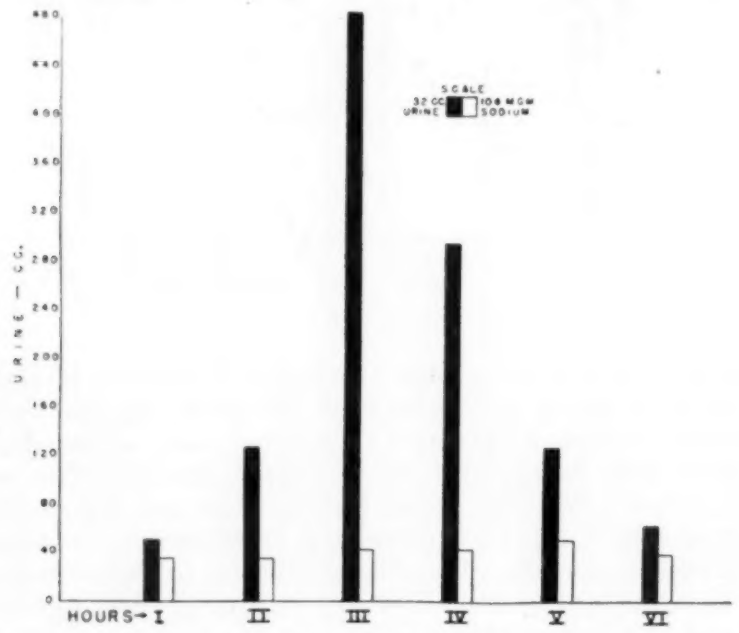

CHART 3. Water diuresis. Urine volume and total renal sodium excretion. Average finding in 32 patients.

In spite of the marked difference in urine volume (799.4 c.c. against 257.4 c.c.) the total renal sodium excretion is actually slightly less during the greatest urine volume period (330.8 mg. against 336.0 mg.). A composite presentation of the average urine volume and total renal sodium excretion for 32 patients over the six hour experimental period is shown in chart 3. As stated above, several of these patients had inadequate urine volume in the control hour, but in spite of this, the group figures show no significant increase in total sodium excretion at the peak of water diuresis. The hour of highest total renal sodium excretion follows the hour of greatest water

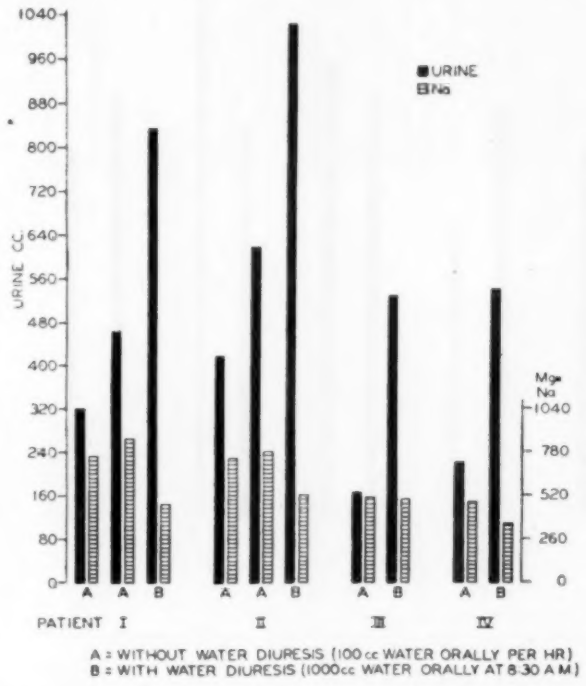

CHART 4. Urine volume and total renal sodium excretion.

diuresis. This may be due to the excretion of the sodium retained during the hours of marked diuresis.

Conceivably, such a reduction in sodium excretion during water induced diuresis could be caused by the post-prandial alkaline tide.[16] However, this factor of food ingestion was reduced as far as possible by doing all tests in the fasting state. Indeed, the occurrence of water diuresis was probably proof that most of the sodium from the upper bowel returned to the extracellular spaces during absorption of the water. It could be argued further that the high sodium excretion during the early hours of this test was secondary to the morning alkaline tide, a condition thought to be associated with the primary carbon dioxide deficit on awakening and for several hours thereafter.[17] Observations were accordingly made on urine volume and

total renal sodium excretion over the same six hour period on consecutive days with and without water diuresis. Chart 4 indicates that total renal sodium excretion under these conditions is again reduced by water diuresis.

It would appear then, that in a patient who already has adequate urine volume, the exhibition of water diuresis does not increase total renal sodium excretion but to the contrary, depresses it. Most of these patients were

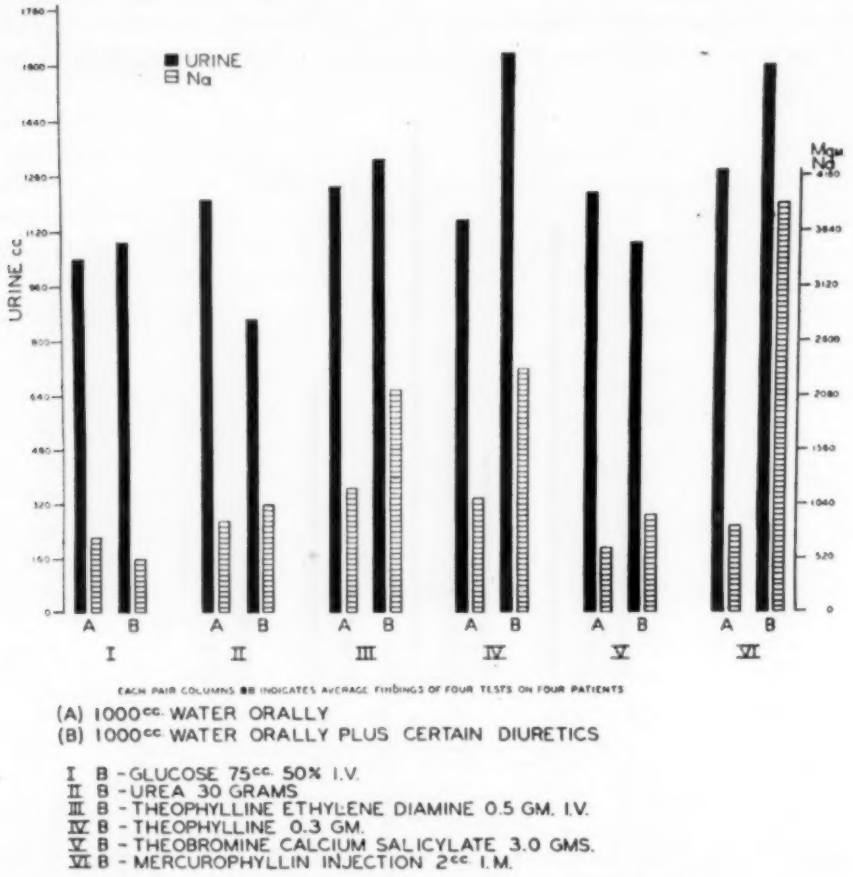
URINE
Na
URINE cc
Mgm Na
A B
I
II
III
IV
V
VI
EACH PAIR COLUMNS BB INDICATES AVERAGE FINDINGS OF FOUR TESTS ON FOUR PATIENTS
(A) 1000cc. WATER ORALLY
(B) 1000cc WATER ORALLY PLUS CERTAIN DIURETICS
I B - GLUCOSE 75cc. 50% I.V.
II B - UREA 30 GRAMS
III B - THEOPHYLLINE ETHYLENE DIAMINE 0.5 GM. I.V.
IV B - THEOPHYLLINE 0.3 GM.
V B - THEOBROMINE CALCIUM SALICYLATE 3.0 GMS.
VI B - MERCUROPHYLLIN INJECTION 2cc I.M.

CHART 5. Urine volume and total renal sodium excretion.

eating a regular diet [15] and therefore, all were excreting approximately 40 to 50 grams of solids in the urine daily.

In the light of the observations recorded the question arises as to optimal water intake for the congestive heart failure patient. Data from patients 3 and 4 in chart 4 suggest that water diuresis depression of renal sodium excretion seems to begin when the urinary flow reaches an equivalent of about two liters in 24 hours. Further data bearing on this point appear in the Group I patients of table 2. Here at a calculated 24 hour urinary output of

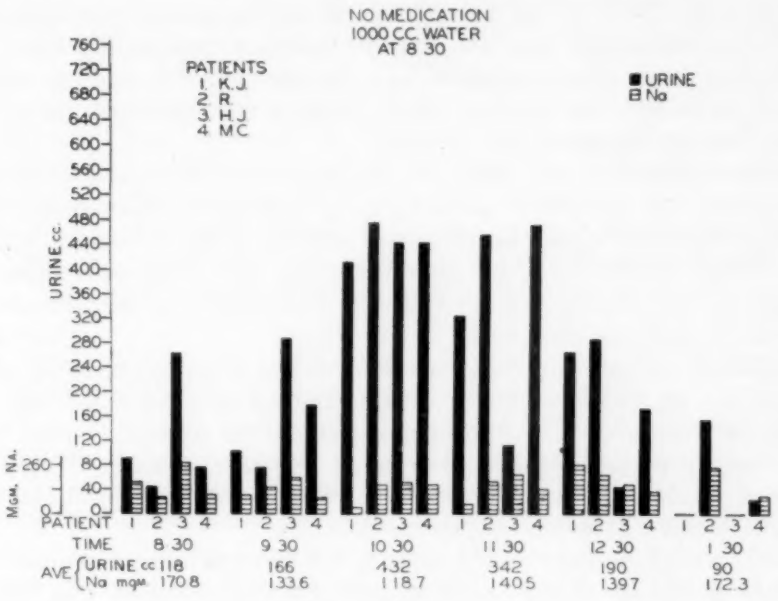

CHART 6 A.

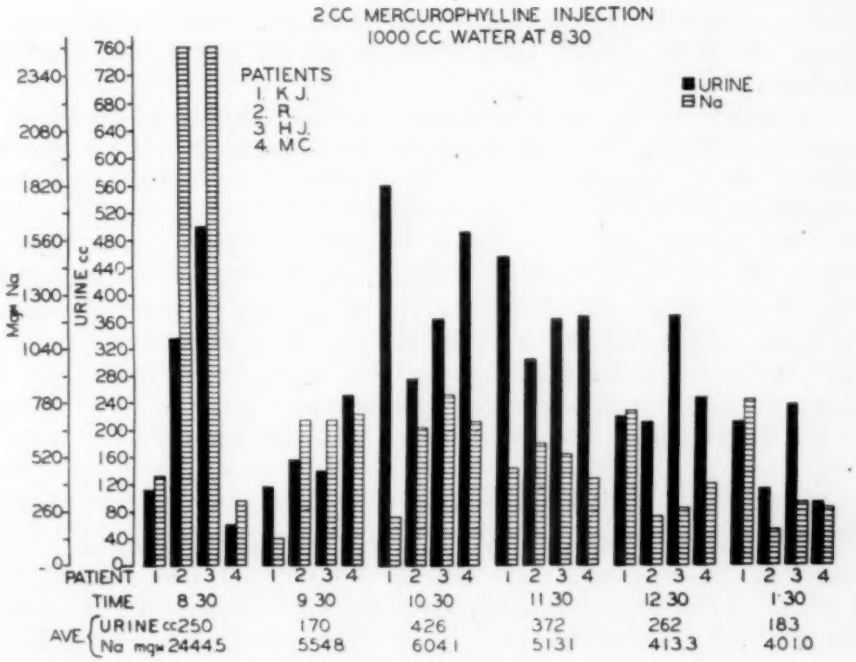

CHART 6 B.

approximately 2904 c.c. total renal sodium excretion was regularly diminished by a still further increase in urine volume. Apparently then, water as a diuretic loses its potentialities as a therapeutic aid in sodium excretion when urine volume has reached a level between two and three liters per 24 hours following increased water intake.

Water Diuresis Plus Certain Diuretics and Renal Sodium Excretion. If this pattern of urine volume and total renal sodium excretion seems reasonably constant for water diuresis then modification of sodium excretion theoretically should follow the administration of diuretic substances at an appropriate time during the experiment. This effect has been observed for a number of common diuretics.

Xanthines: Chart 5 reveals that intravenous theophylline with ethylene diamine is a potent diuretic even when combined with water diuresis. The striking effect, however, was not the relatively small increase in urine volume but rather the great increase in total renal sodium excretion. Theophylline produced similar effects. Theobromine calcium salicylate produced no appreciable increase in sodium excretion.

Mercurophylline Injection: Charts 5, 6 A and 6 B indicate that like intravenously administered theophylline with ethylene diamine, this substance maintained its potency as a diuretic when combined with water diuresis. There was a similar disproportionate increase in urine volume and total renal sodium excretion favoring the latter. The great increase in total renal sodium excretion during the control hour in patients 2 and 3 shown in chart 6 B was due to improper timing of administration of the mercurophylline injection.

Urea and Glucose: As might be expected these osmotic substances tended to lose their efficiency as diuretic agents when combined with a large water intake, as shown in chart 6. In all five of the patients studied, urea seemed to inhibit water diuresis to a slight degree, and correspondingly depressed total renal sodium excretion in three of the five patients. The other two patients showed slight increase in total renal sodium excretion. Glucose produced little effect. In two of the four patients, both water diuresis and total renal sodium excretion were diminished. In the other two, there was slight increase in water diuresis and total renal sodium excretion. The failure of glucose compared with urea may be related to its more rapid removal from the body fluids by oxidation and renal excretion.

Discussion

Water diuresis seems to be based on inhibition of the posterior pituitary gland following relatively rapid dilution of the blood subsequent to water ingestion. It has been shown that water diuresis is associated with decreased total renal excretion of chloride.[29] Our experiments agree with this latter observation as regards sodium in those subjects who had adequate urine volume during the control hour preceding the experiment. The group of

patients (Group II) with inadequate urinary water during the control hour of the experiment increased their total renal sodium excretion during water diuresis.

The explanation for the depression of total renal sodium excretion during water diuresis is not apparent. It does not seem to be directly related to reduced plasma sodium concentration for the greatest plasma dilution as measured by plasma electrolyte concentration precedes the peak of water diuresis by 15 to 30 min.[18] The fact that the greatest depression of renal sodium excretion usually occurs at the peak of water diuresis suggests that the water diuresis and the sodium retention are both mediated through the inhibition of the posterior pituitary.[28] Further evidence to support this thesis is found in the observation that renal sodium excretion is increased by the administration of posterior pituitary substance to normal patients [30] and to animals with diabetes insipidus.[19] Pituitrin in 20 unit doses was tried in several patients during the present study but no striking increase in total renal sodium excretion was observed.

The rôle of the adrenal cortex in this regard stimulates speculation. In view of the known sodium retention effect produced by administration of adrenal cortical extract, it seems possible that the adrenal cortex may be stimulated by the same factor (that is, reduced plasma electrolyte concentration) which inhibits the production of the antidiuretic principle by the posterior pituitary. This point could probably be clarified were it not true that water diuresis cannot be produced in patients with Addison's disease and other hyponatremic states.[13] Regardless of how this depression of total renal sodium excretion is mediated, the kidney apparently conserves sodium, as a prematurely compensatory action, favoring water shift from the intracellular to the extracellular compartment. Such a safety measure insures maximum use of total body water in the face of prolonged diuresis. This particular mechanism has been shown to operate in dogs having experimentally produced diabetes insipidus.[20]

The similarity between the effects of certain xanthine drugs and a mercurial (mercurophylline injection) suggests that these substances have a common mode of action on the kidney, namely, that each depresses tubular reabsorption of sodium more than tubular reabsorption of water.[22, 23] The increase in glomerular filtration rate as an explanation of diuresis following xanthine drugs has been disproved.[31]

In all five patients studied, urea inhibited water diuresis slightly. This seems to be based on a mechanism similar to the well known sodium chloride inhibition of water diuresis.[23, 32] The distribution of urea throughout all body water and its large molecule render it less active than sodium chloride as an inhibitor of water diuresis. In addition to the tendency of glucose and especially urea to inhibit water diuresis these substances are rendered impotent in reducing edema when administered with a large volume of water for they are excreted in the concomitant urinary water without change in the

edema. The effect of urea and glucose on total renal sodium excretion was slight and unpredictable.

Although it is not the purpose of this study to investigate the mechanism or mechanisms underlying the development and maintenance of congestive heart failure, it has been found that many patients with chronic congestive heart failure have a low serum sodium concentration. This is shown by the following values in m. eq. per 1000 c.c. of serum obtained from patients with congestive heart failure: 131.4, 139.1, 135.1, 132.3, 132.7, 138.3, 137.0, 130.1, 137.3, 137.0, 129.6, 138.7, 137.4, and 134.8. These determinations were made in duplicate by the gravimetric method of Butler and Tuthill [21] and may be compared with serum sodium values from normal people in the following series, done at the same time by the same method: 143.5, 142.4, 147.1, 139.8, 141.1, 140.9, and 140.9. That additional factors than the serum sodium concentration influence the amount of sodium excreted during the water diuresis period is indicated by the normal or greater than normal total renal sodium excretion in some of the above patients while serum sodium concentration remained low. The explanation of this low serum sodium concentration in congestive heart failure patients is not apparent. Such factors as prolonged use of a low sodium diet without corresponding restriction of water intake plus use of diuretics which enhance sodium excretion contribute to it.[22, 23, 24, 25] Regardless of the mechanism of its developments, the very presence of low serum sodium concentration tends to cast doubt on retention of sodium as a primary event in the development of congestive heart failure.[26] If such a sequence does occur, naturally one would expect to find serum sodium concentration normal or slightly above normal.[27] On the other hand, with restricted sodium intake the congestive heart failure patient excretes a large intake of water with reasonable facility and this suggests that retention of the sodium ion is of nearer primary importance than retention of water. This matter stands in need of further investigation.

Conclusion

1. It would appear from these data that, in a patient who already has adequate urine volume, the exhibition of water diuresis does not increase total renal sodium excretion. To the contrary, in such a patient, water diuresis usually decreases total renal sodium excretion.

2. It is further suggested that the optimal urine volume for the patient with congestive heart failure, when related to water diuresis alone, falls between two and three liters daily.

3. The efficiency of osmotic diuretics is markedly impaired in edema reduction when combined with water diuresis.

4. Xanthines and mercurophylline injection disproportionately increase urinary volume and total renal sodium excretion favoring the latter. This suggests the primary renal action of these substances may be depression of tubular reabsorption of sodium.

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THE INCIDENCE OF HEART DISEASE IN 2,000 CONSECUTIVE AUTOPSIES *

By WILLIAM B. WARTMAN, M.D.,† *Chicago, Illinois,* and HERMAN K. HELLERSTEIN, M.D.,‡ *Cleveland, Ohio*

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        Atria
    Site of Occlusion
    Correlation of Site of Coronary Occlusion with Infarcts
        Infarcts at a Distance
        Incidence of Occlusion in Cases with Infarcts
        Incidence of Infarcts Following Occlusion
    Factors Concerned in Sudden Death after Coronary Occlusion
        Influence of Hypertension
    Associated Cardiac Lesions (Complications in Infarction)
        Mural Thrombi
        Subsequent Infarcts
        Fibrinous Pericarditis
        Relationship to Muscle Bundles of Heart
        Thromboembolic Phenomena
        Aneurysm of Heart
        Rupture of Heart
    Miscellaneous Heart Diseases
        Syphilitic Heart Disease
        Cor Pulmonale
        Pericarditis
        Cardiac Hypertrophy of Unknown Cause
        Fat Infiltration
        Fatty Degeneration
        Atrophy
        Myocarditis

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Tumors
Valvulitis, Non-rheumatic
Acute Endocarditis
Chronic Non-rheumatic Valvulitis
Air Emboli

THIS report is a statistical study of the incidence of heart disease in 2000 consecutive autopsies performed at the Institute of Pathology, Western Reserve University, from January 28, 1935, to April 4, 1940. These autopsies were on patients who died at Lakeside Hospital (422 beds), Babies and Childrens Hospital (150 beds) and Maternity Hospital (150 beds). All autopsies were performed under the supervision of an experienced pathologist and the final diagnoses were made by him. Anatomical diagnoses were used in making the tables and when it was desirable the diagnoses were checked with the gross descriptions and microscopic slides.

The term "heart disease" is used in an anatomical sense and includes all organic lesions of the pericardium and heart, but it does not necessarily mean clinically evident disease. The criteria set forth by the New York Heart Association [6] are used for both clinical and anatomical diagnoses.

The cardiac lesions were divided into four main groups as follows: (1) Rheumatic heart disease; (2) hypertensive heart disease; (3) coronary artery disease; and (4) miscellaneous. Each of these groups has been subdivided as shown in the tables. Obviously some cases could be put into more than one group, but in order to avoid confusion each case has been listed only once, in the group which was judged to be the most important. For example, nine patients with serious rheumatic heart disease also had mild hypertension. Accordingly, they were classified as rheumatic heart disease.

The group with rheumatic heart disease included only cases with deforming lesions. Not included were cases of chronic non-deforming valvulitis which is now considered as probably due to rheumatic fever.[4]

The group with hypertensive heart disease consisted of patients who during life had persistent elevation of blood pressure and of patients who showed enlargement of the heart with either chronic pyelonephritis, arterial and arteriolar nephrosclerosis or glomerulonephritis. When only terminal blood pressure readings were available the cases were not included unless there was anatomical evidence of previous hypertension. The subgroup "without coronary artery disease" includes cases in which there was either no arteriosclerosis at all or only an occasional intimal plaque which did not obstruct the lumen.

The main group "coronary artery disease, without hypertension" has three subgroups. The first includes cases with slight to moderate arteriosclerosis, associated with myocardial fibrosis; the second, cases with marked stenosis or occlusion due either to arteriosclerosis, thrombosis, intramural hemorrhage or some other cause; the third, cases with endarteritis and periarteritis nodosa. Occlusion is used in the sense of complete obstruction of the lumen.

Age, Sex and Color

Table 1 gives the general incidence of the different anatomical lesions which were discovered at autopsy, and subsequent tables give details of observations in the various groups. Eighty per cent of the 2,000 cases were white, and 20 per cent negro. In each group 64 per cent were males and 36 per cent females. Thirty-six per cent of the patients were under 40 years of age, and 16 per cent of them were under five years. Most of the latter group were premature or newborn babies. The age curve of this series (chart 1) was almost identical with the curve of deaths from all causes in the United States Registration Area for 1940,[12] indicating that our data were representative of deaths in the country as a whole.

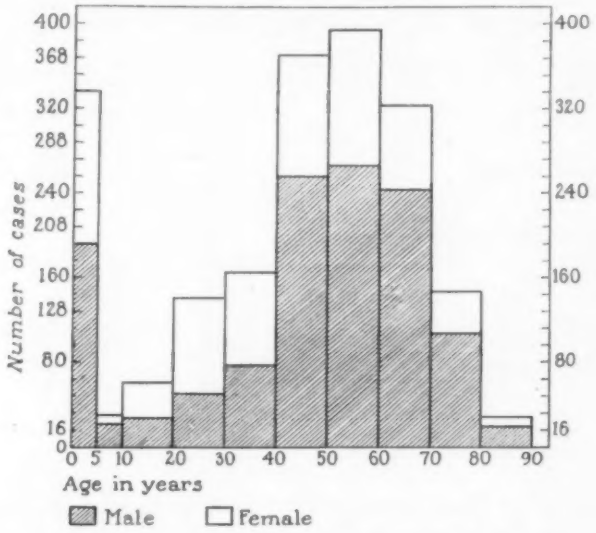

Chart 1. Age, sex distribution of 2,000 consecutive autopsies.

If congenital heart disease is excluded, 984 (49.2 per cent) of the patients had a cardiac lesion (table 1), although not all the lesions were sufficiently important to have contributed to death. Clinical heart failure was noted in 38.9 per cent of these 984 cases (table 2). On the other hand, 505 patients (25 per cent) had heart disease which had been diagnosed clinically, of whom 383 (76 per cent) died with some degree of clinical heart failure. Thus, 76 per cent of those who had clinically evident heart disease had some degree of failure at the time of death, while 19 per cent of the total autopsy group died directly of heart failure.

Comparison of Clinical and Anatomical Diagnoses in Patients Who Died in Heart Failure. Table 3 lists the cardiac lesions in 383 patients who died in failure, and a comparison is made with the clinical diagnoses. Clinical acumen was attested by the high correlation between antemortem and post-

TABLE I

Incidence of Cardiac Lesions in 2,000 Consecutive Autopsies
(Exclusive of Congenital Heart Disease)

	Number of Cases	Per Cent of Cases with Heart Disease	Per Cent of Total Autopsy Population
Rheumatic Heart Disease	120	12.2	6.0
Rheumatic heart disease alone	104	10.6	5.2
Rheumatic heart disease with endocarditis lenta	16	1.6	0.8
Hypertensive Heart Disease	271	27.5	13.6
Without coronary artery disease	77	7.8	3.8
With coronary artery and myocardial disease	194	19.7	9.7
Coronary Artery Disease (without hypertension)	272	27.6	13.6
Coronary arteriosclerosis with myocardial fibrosis	139	13.9	6.9
Stenotic sclerosis, with myocardial fibrosis and infarcts	122	12.4	6.1
Coronary arteritis	11	1.1	0.6
Miscellaneous	321	32.6	16.0
Syphilitic heart disease	20	2.0	1.0
Cor pulmonale	18	1.8	0.9
Pericarditis	52	5.3	2.6
Cardiac hypertrophy, unknown etiology	16	1.6	0.8
Fat infiltration	33	3.3	1.6
Fatty degeneration	30	3.0	1.5
Myocarditis	33	3.4	1.7
Atrophy of heart	19	1.9	1.0
Neoplasm of the heart	16	1.6	0.8
Valvulitis (non-rheumatic)	39	4.0	2.0
Others	45	4.7	2.2
Total	984	100.0%	49.2%

mortem diagnoses in those patients who died in heart failure. There was a tendency to make the diagnosis of arteriosclerotic heart disease in cases of rheumatic heart disease, to overlook myocardial infarcts in hypertensives as well as non-hypertensives, and to diagnose syphilitic heart disease too frequently in rheumatic aortic valvulitis. These results are similar to those of Scott and Garvin.[8]

HYPERTENSIVE HEART DISEASE

Table 4 gives the data for this group. All patients had clinical hypertension and at autopsy a heart which weighed 400 grams or more. Coincident dilatation was present in most cases. Cases of valvular disease with deformity, and nine cases in the group with rheumatic heart disease who also had slight hypertension, were not included.

Only 77 (29 per cent) cases with hypertension had simple uncomplicated enlargement of the heart, whereas 194 (71 per cent) of them had associated coronary artery disease. The incidence of coronary thrombi, myocardial

TABLE II

Incidence of Clinical Heart Failure in Organic Heart Disease Diagnosed at Autopsy

	Number of Autopsy Cases	Clinical Heart Failure	Per Cent Died in Failure
Rheumatic Heart Disease	120	90	75.0
Rheumatic heart disease alone	104	76	73.1
Rheumatic heart disease with endocarditis lenta	16	14	87.5
Hypertensive Heart Disease	271	145	53.5
Without coronary artery disease	77	52	67.6
With coronary arteriosclerosis, with thrombi and infarcts	194	93	47.9
Coronary Artery Disease (without hypertension)	261	100	38.3
Coronary arteriosclerosis, myocardial fibrosis (arteriosclerotic heart disease)	139	40	28.8
Coronary arteriosclerosis with occlusion and infarct	122	60	49.2
Miscellaneous	332	48	14.4
Syphilitic heart disease	20	13	65.0
Cor pulmonale	18	8	44.4
Pericarditis	52	7	13.4
Valvulitis (non-rheumatic)	39	3	7.7
Others	203	31	15.2
Total	984	383	38.9

TABLE III

Comparison of Clinical and Anatomical Diagnoses of 383 Patients Dying in Clinical Heart Failure

	Per Cent Clinical Heart Diagnoses	Per Cent Autopsy Heart Diagnoses
Rheumatic Heart Disease	21.9	23.5
Rheumatic heart disease alone	16.7	19.1
with endocarditis lenta	4.7	3.7
with acute bacterial endocarditis	0.5	0.7
Hypertensive Heart Disease	35.5	37.9
Hypertensive heart disease alone	11.5	13.6
Hypertensive heart disease with coronary arteriosclerosis	12.5	8.6
Hypertensive heart disease with coronary occlusion and infarct	11.5	15.7
Coronary Artery Disease (without hypertension)	27.7	26.1
Coronary arteriosclerosis (arteriosclerotic heart disease)	12.8	10.4
Coronary arteriosclerosis with occlusion and infarct	14.9	15.7
Miscellaneous	14.9	12.5
Syphilitic heart disease	5.7	3.4
Cor pulmonale	2.1	2.1
Pericarditis, constrictive	2.6	1.8
Acute bacterial endocarditis	0.3	0.7
Embolism of right ventricle	0.3	1.0
Thyroid heart disease	0.7	0.0
Others	3.2	3.5

infarcts and fibrosis, which is shown in table 4, needs no comment. Thrombosis without infarction, and infarction without thrombosis will be discussed later. There were 11 cases of valvular disease without deformity and of undetermined etiology in the subgroup "coronary arteriosclerosis with myocardial fibrosis."

TABLE IV

Hypertensive Heart Disease

	Number of Cases
Simple hypertrophy and dilatation *without* coronary arteriosclerosis	77
With coronary arteriosclerosis	52
coronary arteriosclerosis with myocardial fibrosis	37
coronary arteriosclerosis with thrombi and infarcts	62
coronary arteriosclerosis with thrombi, *no* infarcts	3
coronary arteriosclerosis with stenosis and infarcts, *no* thrombi	29
coronary arteriosclerosis with stenosis and myocardial fibrosis	11
Total	271

Referring again to table 2, it is interesting to note that 47.9 per cent of the hypertensive patients who had coronary arteriosclerosis, thrombosis and infarcts, died in clinical heart failure. But as 49.2 per cent of non-hypertensive patients, who had similar coronary artery disease, also died in failure, hypertension evidently did not increase the chances of dying in heart failure in this series.

RHEUMATIC HEART DISEASE

The age, sex and color distribution of 120 cases of rheumatic heart disease are presented in table 5. Eighty-six of these cases had severe valvular deformities and the remainder only slight deformity. Forty-nine cases (41 per cent) of rheumatic carditis lived to be 45 years old or more. This does

TABLE V

Age, Sex, Color Distribution of 120 Cases of Rheumatic Heart Disease
(Includes 16 cases with endocarditis lenta, and 9 cases with hypertension)

Age	White		Colored		Total
	Male	Female	Male	Female	
Under 5 years	1	0	0	0	1
5–14	4	6	2	1	13
15–21	6	2	1	3	12
25–34	11	7	2	3	23
35–44	8	9	2	3	22
45–54	13	8	0	0	21
55–64	7	12	0	0	19
65–74	5	2	1	0	8
75–84	1	0	0	0	1
Total	56	46	8	10	120

not include cases now called healed non-deforming valvulitis.[4] Thirty-four of the cases were active, of which nine were acute and without evidence of previous rheumatic carditis, and 25 had acute verrucous endocarditis superimposed on a chronic process. Involvement of the various valves is shown in table 6. The mitral valve was involved in every case, the aortic in 85,

TABLE VI

Valvular Involvement in 120 Cases of Rheumatic Heart Disease

	Number of Cases
Mitral and aortic	47
Mitral, aortic and tricuspid	26
Mitral alone	18
Mitral and tricuspid	14
Mitral, aortic, tricuspid and pulmonic	11
Mitral, tricuspid and pulmonic	2
Mitral, aortic and pulmonic	1
Mitral and pulmonic	1
Total	120

the tricuspid in 53, and the pulmonic in 15 cases. In 65 cases with severe valvular stenosis, the mitral valve was affected in 62 instances; 31 cases alone, 23 associated with aortic, five with tricuspid and aortic, and three with tricuspid involvement. The aortic valve was attacked in 31 cases; alone three times, with the mitral 23 times, with mitral and tricuspid five times. The tricuspid valve was involved in eight cases only. In no case was there pulmonary stenosis. The frequency of deforming involvement of the valves in rheumatic fever was in the order mitral, aortic, tricuspid and pulmonic. The incidence of coronary arteriosclerosis or thrombosis in this small series apparently did not indicate a trend for precocious occlusive disease in rheumatic fever. The incidence of coronary artery disease (table 7) in 30 per

TABLE VII

Incidence of Coronary Artery Disease in 120 Cases of Rheumatic Heart Disease

	Number of Cases	
With coronary artery disease		36
Rheumatic heart disease with coronary arteriosclerosis	30	
Rheumatic heart disease with coronary thrombi and infarcts	3	
Rheumatic heart disease with coronary emboli, no infarct	1	
Rheumatic heart disease with rheumatic coronary arteritis	2	
Without coronary artery disease		84
Total		120

cent of cases with rheumatic heart disease was almost the same as the incidence of coronary artery disease in the total autopsy group, namely 25 per cent.

ENDOCARDITIS LENTA

Sixteen cases of endocarditis lenta were encountered among the 120 cases of rheumatic heart disease (13 per cent). They were equally divided as to

sex. Thirteen were white, three colored. Thirteen cases fell in the age group 15 to 34 years and the other three cases were between 35 and 54 years. The mitral valve was involved in 13 cases; four cases alone, six with the aortic and three with the aortic and tricuspid. The aortic valve was involved two times alone. The valves were markedly deformed in 11 cases, and slightly in five. There were three cases of myocardial infarcts probably of embolic origin, with no significant coronary artery disease.

Coronary Artery Disease

Cases with coronary artery disease made up the largest group of the series. Counting the cases included in the hypertensive and rheumatic groups, the coronary arteries were significantly diseased in 502 (51 per cent) of the 984 cases with heart lesions or 25 per cent of the 2,000 autopsies.

Table VIII

Coronary Artery Disease (without Hypertension)

	Number of Cases
Coronary arteriosclerosis, uncomplicated	59
Coronary arteriosclerosis with myocardial fibrosis and cardiac hypertrophy	68
Coronary arteriosclerosis with myocardial fibrosis, *without* hypertrophy	11
Coronary arteriosclerosis, with thrombi, infarcts and hypertrophy	50
Coronary arteriosclerosis with thrombi and infarcts, *without* hypertrophy	4
Coronary arteriosclerosis with thrombi, *no* infarcts, with hypertrophy and dilatation	20
Coronary arteriosclerosis, with stenosis and infarcts, and hypertrophy, *no* thrombi	8
Coronary arteriosclerosis with stenosis, myocardial fibrosis, hypertrophy and dilatation	41
Coronary endarteritis obliterans with myocardial infarcts	4
Coronary periarteritis nodosa	3
Coronary arteritis, granulomatous, tuberculous, necrotizing	4
Total	272

Table 8 gives the pertinent data. The group includes (1) all cases with moderate or marked stenosis, and (2) all cases of occlusion whether due to arteriosclerosis, thrombosis, intramural hemorrhage or some other cause.

The heart was enlarged in 187 cases (69 per cent). The incidence was higher in cases with marked coronary artery disease. The sequence of events appeared to be coronary arteriosclerosis, stenosis of the lumen, ischemia of myocardium, dilatation of the heart, myocardial fibrosis, hypertrophy, thrombosis and infarction. There were only four cases with thrombi and infarcts which did not show hypertrophy. There were 14 cases of valvular and endocardial fibrosis without deformity and of undetermined etiology in the subgroup "coronary arteriosclerosis with myocardial fibrosis and cardiac hypertrophy and dilatation."

Myocardial Infarcts and Coronary Occlusion

An analysis was made of the data with reference to the occurrence of myocardial infarcts and of occlusion of the coronary arteries. For the sake of clarity the subject will be discussed under the following headings: (1) Incidence of infarcts; (2) etiology of occlusions; (3) location of infarcts; (4) site of occlusion; (5) correlation of occlusions and infarcts; (6) associated lesions (complications) in the heart.

Incidence. The incidence of myocardial infarcts in the total autopsy group of 2,000 cases was 8.2 per cent. Table 9 shows the incidence of myocardial infarcts in coexistent heart disease based on records of 160 cases which were considered adequate for critical analysis. Table 10 gives the age, sex and color incidence of cases with infarct. In order to evaluate these data it is necessary to know the incidence of males and females in the general autopsy population, as well as in the series under discussion. In the 2,000 consecutive autopsies there were 1280 males and 720 females, a ratio of 1.8 to 1. In the 160 cases in the series, 119 were males (8 colored) and 41 females (9 colored) which is a ratio of 2.9 to 1. There were 143 white and 17 colored patients which is a ratio of 8.4 to 1 in the series of 160, while the ratio in the autopsy population was 4 to 1. With this information the data in table 10 can be summarized as follows: single infarcts were more common in men than women (74 men to 20 women); multiple infarcts were proportionately more common in women than men (45 men to 21 women). Infarcts were relatively more common in colored than white women. Fewer infarcts were found in negroes than would be expected from the race incidence.

Table IX

Incidence of Myocardial Infarcts in Coexistent Heart Diseases

	Number of Cases	
Rheumatic heart disease		3
with coronary thrombi and infarcts	3	
Coronary artery disease (non-hypertensive)		66
Coronary thrombi and infarcts	54	
Coronary arteriosclerosis with infarcts	8	
Endarteritis obliterans with infarcts	4	
Hypertensive heart disease		91
Coronary thrombi with infarcts	62	
Coronary arteriosclerosis with infarcts	29	
Endocarditis lenta		3
Embolic myocarditis with infarcts (No coronary artery disease)	3	
Polycythemia with infarcts		1
Total		164

The relative incidence of hypertension in cases with single and multiple infarcts was the same. The frequent occurrence of hypertension in females with myocardial infarction is consistent with general experience (table 11). Many non-hypertensive women had associated diabetes mellitus and severe generalized arteriosclerosis. In the group of 160 cases, 235 infarcts of the

TABLE X

Age, Sex, Color Incidence in 160 Cases of Myocardial Infarct

Age	White		Colored		Total
	Male	Female	Male	Female	
Single Myocardial Infarct					
25–39	2	1	0	0	3
40–44	2	0	2	1	5
45–54	18	2	1	2	23
55–64	29	4	0	1	34
65–74	14	6	0	0	20
75–84	6	2	0	0	8
85	0	1	0	0	1
Total	71	16	3	4	94
Multiple Myocardial Infarcts					
25–39	0	0	0	0	0
40–44	1	0	1	1	3
45–54	9	2	3	1	15
55–64	17	6	1	2	26
65–74	8	5	0	1	14
75–84	4	3	0	0	7
85	1	0	0	0	1
Total	40	16	5	5	66

myocardium were accurately located by gross dissection. The distribution of infarcts is shown in table 12. Of patients with more than one infarct, 57 had two and nine had three infarcts.

Etiology of Occlusions. Factors which caused occlusion or obstruction of the coronary arteries and resulted in myocardial infarcts are shown in table 13. Most cases in the group "coronary thrombosis" also had moderate to severe arteriosclerosis. The incidence of intramural hemorrhage was about the same as previously reported by Wartman,[10] accounting for 11 per cent of coronary artery obstruction in cases with infarcts.

TABLE XI

Incidence of Hypertension in 160 Cases of Myocardial Infarcts

	White		Colored		Total Cases
	Male	Female	Male	Female	
Hypertensive	54(34%)	24(15%)	7(4%)	8(6%)	93(58%)
Non-hypertensive	57(36%)	8(6%)	1(0.6%)	1(0.6%)	67(42%)
Total	111	32	8	9	160

TABLE XII

Location of 235 Myocardial Infarcts in 160 Patients

Location	Number of Infarcts	Per Cent of Infarcts	Number of Cases	Per Cent of Cases
Right atrium	15	6.4	15	9.4
Left atrium	2	0.9	2	1.3
Left ventricle	196	83.4	152	95.0
Anterior surface of left ventricle	120			
anterior surface, entire	4			
anterior apical	43			
anterior apical and anterior interventricular septum	45			
anterior apical and posterior papillary muscle	3			
anterior apical, lateral	9			
anterior basal, lateral	3			
anterior basal	4			
anterior ventricular septum alone	5			
Lateral surface of left ventricle	8			
Posterior surface of left ventricle	68			
posterior surface, entire	7			
posterior apical	8			
posterior basal	29			
posterior basal and posterior interventricular septum	9			
posterior basal and posterior papillary muscle	2			
posterior interventricular septum	2			
posterior lateral and posterior interventricular septum	11			
Right ventricle	22	9.3	22	13.8
Anterior surface				
anterior surface, entire	2			
anterior apical and anterior interventricular septum	9			
anterior basal	1			
Posterior surface				
posterior basal and posterior interventricular septum	9			
posterior lateral	1			
Total	235	100.0		

Table 14 lists the factors concerned in obstruction (not necessarily accompanied by infarct) of the coronary arteries in the total autopsy group. In 2,000 autopsies there were 247 cases of marked stenosis of one or both coronary arteries, an incidence of 12.4 per cent. In a previous report,[11] the incidence in 6,800 autopsies was 4.4 per cent. This difference is due to more thorough routine dissection of the coronary arteries in the present study.

Location of Myocardial Infarcts. The infarcts were located with reference to the anterior, lateral or posterior, and apical or basal portions of the various heart chambers (table 12) and not with reference to the muscle bundles, because information about muscle bundle localization was not included in the protocols. The left ventricle was the most frequent site of an infarct, being involved in 152 of 160 cases. In the eight cases in which the left ventricle was not involved, infarcts were present in the right atrium and right ventricle in four cases each.

TABLE XIII

Causative Factors in 164 Cases of Myocardial Infarcts

	Number of Cases	Per Cent of Cases
Coronary thrombosis	101	61.6
Coronary thrombosis and myocardial infarcts		
in group coronary artery disease	43	
in group hypertensive heart disease	55	
in group rheumatic heart disease	3	
Intramural hemorrhage	18	11.0
Intramural hemorrhage and myocardial infarcts	11	
Intramural hemorrhage, thrombosis and infarcts	7	
Coronary arteriosclerosis without thrombosis	41	25.0
Endarteritis obliterans	4	
Occlusive arteriosclerosis with infarcts	13	
Marked stenotic arteriosclerosis with infarcts	13	
Mild to moderate sclerosis with infarcts	11	
Polycythemia	1	2.4
Endocarditis lenta (mycotic infarct)	3	
Total	164	100.0

The anterior half of the interventricular septum was involved in 54 per cent of cases which had an infarct of the anterior portion of the left ventricle. When the infarct was posterior, 25 per cent showed involvement of the posterior half of the interventricular septum. In five cases the interventricular septum was involved alone. The lateral aspect of the left ventricle was seldom involved alone, for of 33 cases, 25 occurred in combination with infarcts of the anterior-apical or posterior-basal areas (76 per cent). In 21 cases infarcts were located in both anterior-apical and posterior-basal regions. In each case one infarct was fresh and the other old.

Infarcts were found in the right ventricle in 22 cases (13.8 per cent). These cases have been divided into three groups: (1) pure, four cases; (2)

TABLE XIV

Factors Concerned in Obstruction of the Coronary Arteries in 2,000 Consecutive Autopsies

Lesion	Number of Cases	Per Cent of Cases
Embolism	1	0.4
Inflammation	13	5.3
Rheumatic arteritis	2	
Periarteritis nodosa	7	
Endarteritis obliterans	4	
Syphilis (stenosis of coronary ostia)	2	0.8
Coronary thrombosis (alone or with intramural hemorrhage)	142	57.5
Coronary arteriosclerosis with stenosis *	89	36.0
With myocardial infarcts	37	
Without myocardial infarcts	52	
Total	247	100.0

* Stenosis means reduction in diameter of lumen to one-half or less.

overflow, or extension from the left ventricle, eight cases; and (3) mixed, 10 cases. In group 1, the sole lesion was in the right ventricle. Two cases were fresh, one old, and one case had both old and recent infarcts. Two were in the anterior apical area with extension into the anterior portion of the interventricular septum, one in the posterior-basal area with extension into the posterior portion of the interventricular septum, and one case in the posterior lateral region. In each case the main right coronary artery was involved. Group 2 included the cases in which the main area of infarct was

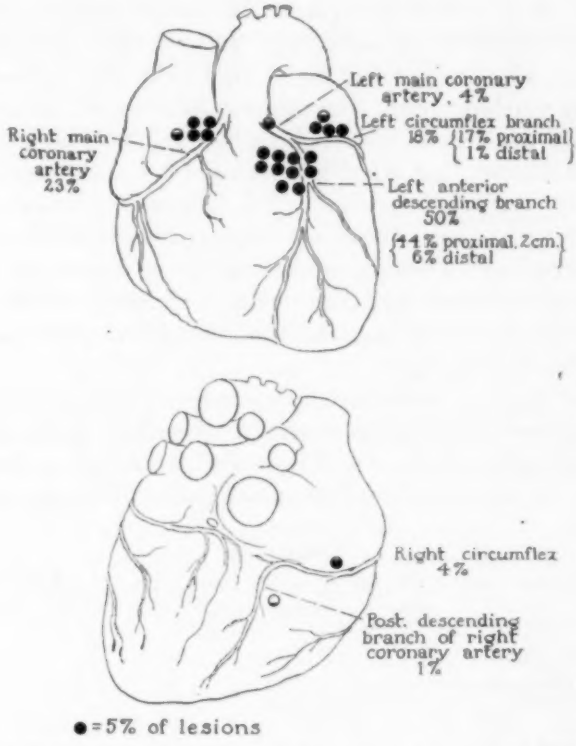
Left main coronary artery, 4%
Left circumflex branch 18% {17% proximal 1% distal}
Right main coronary artery 23%
Left anterior descending branch 50% {44% proximal, 2cm. 6% distal}
Right circumflex 4%
Post. descending branch of right coronary artery 1%
●=5% of lesions

CHART 2. Sites of 207 occlusions in 132 cases of myocardial infarction.

in the left ventricle, and the contiguous adjacent right ventricle was involved for a distance of 0.5 to 2 cm. The distribution of the eight cases in which both ventricles were so involved was: five in the anterior apical portion and anterior interventricular septum, and three in the posterior basal portion. Six infarcts were new and two old. Group 3 consisted of 10 cases with both overflow and separate infarcts of the right ventricle; in other words, a combination of groups 1 and 2. In five cases the infarct in the right ventricle was the same age as the infarct in the left ventricle. The distribution of the separate infarcts was: five cases posterior basal, one anterior basal, two anterior apical, and two entire anterior surface. The right coronary artery

was occluded in each case, in addition to the occlusion of the afferent artery of the infarct in the left ventricle. In three cases, the right coronary artery was predominant, supplying the posterior surface of the left ventricle. There were old recanalized lesions in the right main coronary artery and old infarcts of the anterior right ventricle, and a recent thrombus in the distal portion of the right circumflex branch with a recent infarct of the posterior basal portion of the left ventricle.

Infarcts of the atria occurred 17 times (7.2 per cent), twice in the left and 15 times in the right chamber. Of the 17 cases, 13 showed other infarcts in the left ventricle of which 10 were in the anterior-apical and three in the anterior-apical and posterior-basal areas. In four cases only an atrial infarct was discovered. The incidence of atrial infarcts in this series is lower than that reported by Cushing, Feil, Stanton and Wartman [2] who found infarcts in the atria in 17 per cent of cases which had ventricular infarcts. This is probably due to the fact that atrial lesions were not specifically looked for in the early cases in the present series. The preponderance of infarcts in the right atrium which has been previously reported [2] was confirmed.

Site of Occlusion. Definite occlusions were found in the coronary arteries of 132 of 160 cases (82.5 per cent) of infarcts of the myocardium. These cases will be discussed first and the 28 cases in which occlusions were not found will be taken up later.

The various types of lesions which caused occlusion will be found in table 9 and have been discussed previously. Chart 2 shows the sites of 207 occlusions which were found in 132 hearts with infarcts. Eighty-eight per cent of the lesions occurred in the proximal parts of the main arteries, i.e.,

TABLE XV

Distribution of Arterial Occlusions in 132 Cases with Myocardial Infarcts

Artery	Number of Cases
Left anterior descending coronary artery	46
Left anterior descending, and right main	21
Right main	16
Left circumflex	13
Left circumflex and left anterior descending	13
Left circumflex and right main	4
Left circumflex, right main, and left anterior descending	4
Left main	1
Left main and left anterior descending	2
Left main, left anterior descending, left circumflex	1
Left main, left anterior descending, right main	1
Right circumflex	2
Right circumflex, left anterior descending	3
Right circumflex, left circumflex	1
Right circumflex, right main, left anterior descending	1
Right posterior descending	1
Right posterior descending, left circumflex	1
Right posterior descending, left circumflex, left anterior descending	1
Total	132

main left, proximal 4 cm. of the main right, proximal 2 cm. of left circumflex and left anterior descending artery. These data need no comment for they conform to the general experience.

Table 15 shows the various combinations of arterial occlusions. It is interesting to note that the right coronary artery, either alone or in combination with other arteries, was implicated in 35 per cent of all cases. Both main coronary arteries were occluded in 37 cases. Two major branches of the left coronary artery were occluded in 22 cases. Table 16

TABLE XVI

Comparison of Distribution of Arterial Occlusions by Per Cent of Lesions and Per Cent of Cases

	Left Ant. Descending	Right Main	Left Circumflex	Right Post. Descend.	Left Main	Right Circumflex
Per cent lesions	50	23	18	1	4	4
Per cent cases	70	35	22	2	4	5

shows the distribution of arterial occlusions by per cent of lesions, and by per cent of cases. Fifty per cent of the lesions were in the left anterior descending artery, while 70 per cent of the cases had occlusion of this artery. The high incidence of multiple occlusions in several major coronary arteries (table 15) in the same patient explains this difference in percentage.

Correlation of the Sites of Coronary Occlusion and Myocardial Infarcts. Generally speaking, solitary occlusion of the anterior descending branch of the left coronary artery led to an infarct in the anterior-apical portion of the left ventricle and interventricular septum. There were 52 cases of this sort. In addition, there were 20 cases in which, despite occlusion of several arteries, the only infarct discovered was in the location just described. In nine of these cases the main right and the left descending coronary arteries were completely obstructed. It seems probable that there was predominance of the right coronary artery in these cases so that occlusion of this vessel resulted in an infarct at a distance. That is to say, there had been an old occlusion of the left descending coronary artery without resulting infarct, but when the main right coronary artery was occluded, then a fresh infarct, which was at a distance from the most recent obstruction, developed at the apex of the left ventricle. Infarcts of the apex of the heart were encountered with other combinations of occlusions such as all three main branches, and the descending and circumflex branches of the left coronary artery. In one case, there was occlusion of the main right coronary artery with infarction at a distance of the anterior-apical part of the left ventricle.

Solitary occlusion of the proximal circumflex branch of the left coronary artery resulted in infarcts in the posterior lateral portion of the left ventricle in four cases, and in the posterior basal area in nine cases. Nevertheless, the most common artery which was occluded in cases with posterior basal

infarcts of the left ventricle was the main right coronary artery (12 cases), indicating that in these hearts too, the right coronary artery was probably predominant. In several cases posterior basal infarcts of the left ventricle were found in hearts with multiple occlusions in the main right and left circumflex arteries.

Whenever an infarct was found in the right ventricle alone the main right coronary artery was occluded. When the anterior apical portion of the right ventricle was involved contiguously the descending branch of the left coronary artery was also occluded. All cases with infarcts in the posterior-lateral and posterior-basal areas of the right ventricle had occlusions in the main right coronary artery, and in several instances the circumflex branch of the left coronary artery was also involved.

Multiple infarcts of the anterior-apical and posterior-basal areas of the left ventricle had complete obstruction of both the descending branch of the left and the main right coronary arteries in 12 cases, and of the descending and circumflex branches of the left coronary artery in four cases.

At this point, it is appropriate to emphasize that, although an infarct is frequently found close to the occluded artery, which is usually the predominant artery for that area, this is not always true, and infarcts may be discovered at a distance from the affected artery.[7] For this reason, it is preferable from the clinical viewpoint to diagnose the site of an infarct rather than the artery which is supposedly obstructed.

Coronary Occlusion in Cases of Myocardial Infarction. Complete occlusion, due either to thrombosis, embolism or arteriosclerosis, was found in 132 (82.5 per cent) cases of myocardial infarction. In another nine cases (5.6 per cent) there was coronary arteriosclerosis with stenosis of such marked degree as to account for the infarcts which were discovered in the left ventricle. An additional four cases (2.5 per cent) with stenosing arteriosclerosis had infarcts in the atria only. Cushing, Feil, Stanton and Wartman [2] have previously reported that in a high percentage of atrial infarcts an occlusion is not found. Small multiple infarcts were found in one case of polycythemia and in three cases of endocarditis lenta there were small mycotic infarcts.

Thus 11 cases (6.9 per cent) remained in which no occlusive lesion was discovered despite the presence of infarcts. Severe arteriolar sclerosis was noted in several cases, but in six cases (3.8 per cent) no explanation for the infarcts was found.

Myocardial Infarcts in Cases with Coronary Thrombosis. Myocardial infarcts were discovered in 84 per cent (119) of patients with coronary thrombosis (table 17), leaving 16 per cent (23) who died of coronary thrombosis without myocardial infarcts. Only three of these were hypertensive. Fourteen of the 23 patients died suddenly, within three hours of the earliest onset of clinical symptoms, before morphological infarcts could be expected to develop. Twelve were above 50 years of age, two between 40

and 50 years. Thirteen were males and one was a female. All were white. In the series of 160 cases the ratio of males to females was 1.9 to 1, and white to black 4 to 1. Every case of sudden death had generalized coronary arteriosclerosis with marked stenosis. Five cases had multiple recent and old occlusions of the major rami. The left coronary was involved in eight cases, the right coronary artery in six cases. Specifically the vessels involved were: left main and left anterior descending, three cases; left anterior descending, three cases; right main, three cases; right main, left anterior descending and left circumflex, one case; right circumflex and left anterior descending, one case; right circumflex, one case; left main, one case; and left circumflex, one case. A notation was made in several cases in which the occlusion was in the main right artery, that the greater part of the posterior

TABLE XVII

Incidence of Myocardial Infarcts in Cases with Coronary Thrombi

	Number of Cases	Per Cent of Cases
Thrombi with infarcts	119	84
With hypertensive heart disease	62	
With arteriosclerotic heart disease	54	
With rheumatic heart disease	3	
Thrombi without infarcts	23	16
With hypertensive heart disease	3	
With arteriosclerotic heart disease	20	
Total	142	100.0

surface of the heart was supplied by that artery, that is, the right coronary was predominant.

Sudden Death. In this study, the factors concerned in sudden death following coronary thrombosis were: (1) Severe generalized coronary arteriosclerosis; (2) multiple occlusions with involvement of the predominant artery; (3) males were more susceptible than females; (4) whites more than negroes; (5) age was apparently not an important factor.

Of the nine patients with thrombosis without infarction in whom sudden death did not occur, six had old thrombi without infarcts. Possibly a collateral circulation had prevented the development of infarcts. Three cases had recent thrombi which according to the clinical history were of two to three days' duration. All nine cases had marked generalized stenosing coronary arteriosclerosis. The distribution of lesions was as follows: In three cases the left anterior descending branch was involved, in three cases the right main coronary, in two the left circumflex, and in one case there was a recent occlusion of both left anterior descending and circumflex as well as an old one in the right main coronary artery. The causes of death in these nine cases were: pneumonia, four cases; pulmonary embolism, one case; peritonitis, two cases; and heart failure, two cases. The age distribution was similar to the group that died suddenly of coronary thrombosis. Eight were above 50 years of age and one was 42 years old.

To summarize the above, 16 per cent of cases with coronary thrombosis did not develop myocardial infarcts. Ten per cent died quickly before an infarct could reasonably be expected to develop. Since 58 per cent (93) of patients with myocardial infarcts were hypertensive, and only 13 per cent (3 of 23 cases) with coronary thrombosis but without myocardial infarcts were hypertensive, it appeared that arterial occlusion produced infarcts in hypertensives more readily than in non-hypertensives. Furthermore, coronary thrombosis caused sudden death more frequently in non-hypertensive patients. Thirteen of 14 patients (93 per cent) who died suddenly were non-hypertensive, whereas 42 per cent of the series was non-hypertensive.

Associated Cardiac Lesions (Complications) in Myocardial Infarction

The most common cardiac complications of myocardial infarction were: mural thrombi, subsequent infarcts, acute fibrinous pericarditis, aneurysm formation, and rupture of the heart.

Of 160 cases with myocardial infarcts, 40 per cent (64 cases) had *mural thrombi*. This incidence agrees with reports in the literature.[1] Of 94 cases with single myocardial infarcts 32 (34 per cent) had mural thrombi, of which 22 were fresh and 10 old. In 66 cases of multiple myocardial infarcts, 32 cases (48.5 per cent) had mural thrombi of which six had multiple old infarcts, three multiple recent, and 23 recent and old infarcts. Thus multiple repeated episodes of infarction seemed to increase the chances of mural thrombosis. The location of the intracardiac thrombi was always directly beneath the infarct. In 44 cases the thrombi were in the anterior portion of the left ventricle, in 10 cases in the posterior basal portion, in 14 cases in the right auricle, and in four cases in the right ventricle. In eight cases there were mural thrombi in both ventricle and auricle.

Subsequent Infarcts. The tendency for patients with one infarct to develop subsequent lesions is indicated by table 18. Fifty-one cases (32 per cent) had both fresh and old infarcts. In 10 cases there were multiple recent infarcts which were not all of the same age.

Acute fibrinous pericarditis was found in 31 of 111 cases (28 per cent) with recent myocardial infarcts and was localized over the myocardial lesion. Twenty-two (71 per cent) of these 31 cases also had mural thrombi. This common association of fibrinous pericarditis and mural thrombosis is not surprising when the anatomy of the heart muscle bundles is considered. The apex of the heart, which was the site of the infarct in over 66 per cent of all cases, is composed of two relatively thin layers of muscle, namely, the superficial sino-spiral and superficial bulbo-spiral muscles. These muscles make up the full thickness of the apical fourth of the left ventricle and twist around at the apex to pass upward and form the subendothelial surface and papillary muscles of the left ventricle.[5] Infarcts in this area usually involve both superficial muscles and hence the entire thickness of the heart wall,

predisposing to both pericarditis and thrombosis. In a few cases pericarditis and mural thrombi were also found in the posterior basal portion of the left ventricle. Often the subepicardial and subendocardial muscle in this region were the seat of infarction, the middle layer of muscle being spared. This denoted involvement of the superficial bulbospiral muscle, part of which is superficial (subpericardial) and part deep (subendocardial). Mural thrombi were also common in cases with atrial infarcts. This is probably explained by the fact that the atria are composed of thin muscle bundles.[6] Thus, patients with infarcts in the apex of the heart or in the atria may be expected to show thrombo-embolic phenomena. Fifty-five per cent of cases with intracardiac thrombi had occlusions of peripheral vessels from either thrombi or emboli. Thirty-nine per cent of cases without mural thrombi

TABLE XVIII

Chronology and Multiplicity of Myocardial Infarcts in 160 Cases

Number of Infarcts	Recent	Old	Recent and Old	Total Number of Cases
Single	50	44	—	94
Multiple	10	5	51	66
Total	60	49	51	160

had similar lesions. Emboli in the peripheral circulatory system with distant infarcts were a main or contributory cause of death in 43 of 160 patients (27 per cent).

Aneurysm formation occurred in 35 cases of myocardial infarcts. Cases with diffuse dilatation of the ventricle were not included, but only those with more or less well circumscribed dilatation involving the area of infarction. There was a higher incidence of aneurysm in cases with multiple infarcts (26 per cent) than in cases with single infarcts (19 per cent). Aneurysms developed progressively in the site of the infarct. This was shown by the fact that of 60 cases with a recent infarct, seven (12 per cent) had aneurysms; of 49 cases with an old infarct, 14 (29 per cent) had aneurysm, and of 51 cases of both recent and old infarcts 14 (28 per cent) had aneurysms. Mural thrombi and acute fibrinous pericarditis were a common accompaniment. Seventeen (49 per cent) of the 35 cases had mural thrombi and 10 (59 per cent) of the 17 cases had both mural thrombosis and pericarditis. Four (11 per cent) of the cases had pericarditis alone. The possible clinical significance of these observations are apparent: about half of the cases with myocardial aneurysm had mural thrombi. Seventy-one per cent of cases with myocardial aneurysm and pericarditis also had mural thrombi.

The aneurysms occurred in the same areas where infarcts were most frequent, i.e., 25 cases anterior apical, three cases posterior and lateral, and

seven cases posterior basal portion of the left ventricle. In three of the 25 cases of anterior apical infarction and aneurysm formation, the interventricular septum was also involved and bulged into the right ventricle. Rupture occurred in five of 35 cases (14.3 per cent) of cardiac aneurysm.

Cardiac Rupture. There were seven cases of cardiac rupture in the 160 cases of myocardial infarcts (4 per cent). Six of the 111 cases of recent infarcts ruptured at the site of the recent lesion; the other case occurred in an aneurysm in an old posterior basilar infarct of the left ventricle. Rupture occurred in the anterior wall of the left ventricle near the apex in four cases, and in three cases in the posterior basal portion of the left ventricle.

In this series rupture occurred at the site of an aneurysm in five of seven cases. In the cases of recent infarct, five ruptured from two to seven days, and one on the eighteenth day after the onset of clinical symptoms. Apparently the size of the infarct did not play a dominant rôle, since in only one case was the infarct massive. Lowe and Wartman[5] have shown that both aneurysm and rupture are determined in large part by the number of muscle bundles which are involved. If an infarct involves the full thickness of the wall, that is, if two or more muscle bundles are affected, the muscle may break as soon as granulation tissue appears. However, if only a portion of the thickness of the wall is involved, as when a single bundle is necrotic, rupture occurs less and aneurysm more frequently. Increased intraventricular pressure, absolute or relative, probably plays a rôle also.[3]

Miscellaneous

Syphilitic Heart Disease. This group consisted of 20 cases of syphilitic aortic valvulitis. There was syphilitic aortitis in all cases and aortic aneurysm in 11. The coronary ostia were stenotic in two cases. Heart failure caused death in 13 cases. The average weight of the heart in the entire group was 532 grams; of those who died in heart failure it was 626 grams; and of those who died of other causes 360 grams.

Cor Pulmonale. There were 18 cases with hypertrophy of the right ventricle. Associated pulmonary diseases included bronchiectasis, silicosis, chronic bronchitis, emphysema, and congenital cystic disease of the lungs. There was one case of enlargement of the right heart and failure secondary to marked kyphoscoliosis. The average heart weight was 420 grams. Two cases had systemic hypertension. Failure of the right side of the heart occurred in eight cases.

There were four cases of embolism into the right ventricle, resulting in acute cor pulmonale and sudden death. The right ventricle was dilated and distended by the coiled embolus. In two cases the embolus appeared to originate from pelvic veins, six and seven days after an operation; and in two cases from the site of fractures of the femur and pubis at the time of manipulation and reduction. However, the veins of the lower extremities were not regularly explored.

Pericarditis. This group included 32 cases of acute fibrinous and 20 cases of healed pericarditis. Pericarditis due to rheumatic heart disease or myocardial infarct was not included in this group, but in the respective groups. Twenty-five cases of fibrinous pericarditis due to uremia were included in the group "hypertensive heart disease."

Acute pericarditis, fibrinous, serofibrinous or fibrinopurulent, occurred secondary to the following diseases in this order of frequency: uremia, myocardial infarcts, rheumatic pancarditis, pneumonitis (lobar and bronchopneumonia), septicemia, and carcinoma of the lung.

There were 20 cases of chronic pericarditis of which five were constrictive. Two of the five were tuberculous in origin. Three had been surgically decompressed, of which one patient survived two years and died of other causes. Of the two cases which were not operated on, one died of cardiac insufficiency. The heart weight of 14 of the cases ranged between 250 and 350 grams. In six cases, the heart was enlarged with an average weight of 530 grams. There was associated hypertension in two cases, valvular deformity in one case, and mediastinal-diaphragmatic adhesions in three.

Cardiac Hypertrophy of Unknown Cause. This group included 16 cases of cardiac hypertrophy of unknown cause (non-hypertensive, non-arteriosclerotic, non-valvular). Three were children with hearts weighing 30 to 59 per cent above the expected weight (one leukemia, two pneumonia). The average weight of the 13 adult hearts was 440 grams.

Fat Infiltration. This group included 33 cases of moderate and marked fat infiltration of the heart without coronary artery or valvular disease. The ratio of females to males was 1.5 to 1 whereas the ratio of females to males in the whole autopsy group was 0.6 to 1, suggesting a greater incidence in females. No significant difference in heart weights existed in males and females, the average weight being 350 and 325 grams respectively. The average body weight of males was 59 kilograms, and of females 63 kilograms. Moderate fat infiltration occurred in some cases of severe emaciation. In one case there was slight cardiac decompensation.

Fatty Degeneration. Fatty degeneration occurred in 30 cases, three pernicious anemia, four myeloid leukemia, four uremia, eight carcinomatosis, two diabetes mellitus, five chronic pulmonary infections, and four chronically decompensated arteriosclerotic heart disease. In two cases, mild cardiac decompensation occurred in the absence of hypertension, coronary artery or valvular disease. However, not all hearts were stained for fat.

Atrophy of the Heart. Atrophy of the heart occurred in 19 cases, all of which had wasting diseases. Fourteen cases were secondary to widespread metastases (carcinoma of the stomach four, colon two, lung, liver, breast, esophagus each one case, and undetermined primary source four cases). Five cases occurred in chronic ulcerative pulmonary and peritoneal tuberculosis, Hodgkin's disease and Simmonds' disease. The hearts were uni-

formly small, with average weight of 198 grams, ranging from 140 to 240 grams. The muscle fibers were small, with droplets of brown pigment at the ends of nuclei. The subepicardial fat was sparse and the seat of serous atrophy. The coronary arteries were tortuous, owing to shrinkage of the myocardium. In only one case was there systemic hypertension, 150 mm. mercury systolic and 100 mm. diastolic, and the heart weighed 210 grams.

Myocarditis. This group included 16 cases of acute, 14 subacute, and three chronic myocarditis. The 16 cases of acute myocarditis consisted of 10 cases of acute diffuse, two of acute focal, three of acute interstitial, and one of acute suppurative myocarditis. The average weight of the heart in acute interstitial myocarditis was 290 grams. Acute diffuse myocarditis occurred in three cases of pneumonia, in three cases of septicemia due to erysipelas, infected abortion and impetigo, in two cases of brain tumor, in two cases of pulmonary and intestinal tuberculosis. There were two cases of focal myocarditis of the right ventricle in pneumonia, and atrophic arthritis. Suppurative myocarditis was found postoperatively after decompression of a patient with constrictive pericarditis. Subsequent rupture of the heart caused death.

Subacute myocarditis occurred in 14 cases; seven cases had acute infections, pneumonia, suppurative otitis media and mastoiditis; one case occurred in each of the following: uremia, acute hepatic necrosis, intestinal obstruction, myasthenia gravis, carcinoma of the stomach, cirrhosis of the liver, and cause unknown. The process was focal in the right ventricle in three cases.

The three cases of chronic myocarditis occurred in uremia, tuberculosis of the spine and meningococcemia.

Neoplasm of the Heart. Sixteen cases had neoplasms of the heart, of which one was a primary leiomyosarcoma of the right atrium with direct extension into the superior vena cava, left subclavian vein, and myocardium of the right ventricle and left atrium. Metastases were found in lungs and adrenals.

Primary tumors which metastasized to the heart were: lung six cases, pancreas three cases, stomach two cases, lymphoblastoma three cases, breast one case. The tumors were all poorly differentiated. The visceral and parietal pericardia were involved in 10 cases, and pericardium, endocardium and myocardium in five cases. Cardiac symptoms due to tumor metastases occurred in four cases. Antemortem diagnosis of tumor metastasis to the heart was made in one case. In one case of carcinoma simplex of the lung, metastases to the posterior portion of the left ventricle caused symptoms of infarction and electrocardiographic changes suggestive of a posterior basal infarct. In a case of squamous cell carcinoma of the right bronchus, rupture of the right ventricle occurred at the site of metastases.

Valvulitis (Non-Rheumatic). This group included 10 cases of acute bacterial endocarditis, 12 cases of thromboendocarditis and 17 of chronic non-rheumatic valvulitis.

Acute Vegetative and Ulcerative Bacterial Endocarditis. The bacteria responsible in five cases were pneumococci, one case *Streptococcus viridans*, and four cases undetermined. Five cases had lobar pneumonia, three cases septicemia originating in osteomyelitis of the frontal sinuses and sacrum, one case from secondarily infected carcinoma of the colon, and in one case the site was undetermined. The aortic valve was involved in seven cases, the mitral in three, the tricuspid in two and the left atrial endocardium in one case. In three cases acute bacterial endocarditis occurred in the aortic valve of a heart with healed non-deforming endocarditis of the mitral, aortic and tricuspid valves. In one case an aortic leaflet ruptured.

Thromboendocarditis occurred in 12 cases, seven non-rheumatic verrucous endocarditis, three endocarditis minima, two atypical verrucous endocarditis. The valves were involved in the order mitral seven cases, aortic six, tricuspid one, pulmonic one.

Chronic Non-Rheumatic Valvulitis. In 14 cases there was healed non-deforming endocarditis involving mitral, aortic and tricuspid valves in that order of frequency. In three cases there was in addition calcific aortic stenosis. It is possible that stigmata of associated rheumatic disease would be found upon reëxamination of these cases.[12, 4]

Air embolism occurred during an operation on a tumor of the neck involving the right subclavian vein and resulted in immediate death.

Trauma. Contusion of the heart occurred in a graze bullet wound, and chest injury. In both cases death was due to cardiac decompensation.

Summary

The protocols of 2,000 consecutive autopsies performed at the Institute of Pathology, Western Reserve University, from 1935 to 1940, were reviewed in order to determine the incidence of the various diseases of the heart. Eighty per cent were white, and 20 per cent negro; 64 per cent males and 36 per cent females. The age curve of this series was similar to that of deaths from all causes in the United States Registration Area for 1940. Forty-nine and two tenths per cent of the patients had some cardiac lesion at autopsy, although not all were sufficiently important to have contributed to death. Nineteen per cent of the total autopsy population died directly of heart failure.

The cardiac lesions were divided into four main groups: rheumatic heart disease, hypertensive heart disease, coronary artery disease, and a miscellaneous group. Thirteen and six tenths per cent of the autopsy group had hypertensive heart disease. The chance of dying in heart failure was not increased by hypertension for patients with coronary arteriosclerosis, occlusions and infarcts.

The age, sex, color distribution of 120 cases of rheumatic heart disease was presented. The mitral valve was involved in every case, and aortic in 85, the tricuspid in 53 and the pulmonic in 15. Forty-nine (41 per cent)

cases of rheumatic carditis lived to be 45 years old or more. There were 16 cases of endocarditis lenta among the 120 cases of rheumatic heart disease (13 per cent).

The coronary arteries were significantly diseased in 51 per cent of the 984 cases with heart lesions, or 25 per cent of the total autopsy series. The heart was enlarged in 69 per cent of cases with coronary artery disease. The importance of arteriosclerosis, thrombosis and intramural hemorrhage in producing occlusion of the coronary arteries is discussed. Eighty-four per cent of the lesions occurred in the proximal parts of the main arteries. Multiple occlusions were found in many cases. The right coronary artery was implicated in 35 per cent; the left anterior descending artery in 70 per cent of all cases. Eighty-four per cent of cases with coronary thrombosis also had myocardial infarcts, 16 per cent died without myocardial infarcts, many of them suddenly, within three hours of the earliest onset of clinical symptoms and before morphological infarcts developed. The factors concerned in sudden death following coronary obstruction were severe generalized coronary arteriosclerosis, and multiple occlusions with occlusion of the predominant artery. Age was apparently not an important factor.

The incidence of myocardial infarcts in the total autopsy series was 8.2 per cent. The pertinent data were analyzed as to incidence, etiology of occlusions, location of infarcts, site of occlusion, correlation of occlusion and infarcts, and associated lesions in the heart. Single infarcts were more common in men than women; multiple infarcts were proportionately more common in women than men; infarcts were relatively more common in colored than white women; fewer infarcts were found in negroes than would be expected from the race incidence. The left ventricle was the most frequent site of an infarct; infarcts were also found in the right ventricle, and both atria. The problem of infarction at a distance is discussed.

The most common cardiac complications of myocardial infarction were mural thrombi (40 per cent), fibrinous pericarditis (28 per cent of recent myocardial infarcts), subsequent myocardial infarcts (32 per cent), aneurysm formation (22 per cent), and cardiac rupture (4 per cent). Peripheral thrombo-embolism occurred in 45 per cent of cases of myocardial infarcts, and were a main or contributory cause of death in 43 of 160 cases.

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RHEUMATISM AND ARTHRITIS

REVIEW OF AMERICAN AND ENGLISH LITERATURE OF RECENT YEARS

(Ninth Rheumatism Review) *

Part I

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The last Review prepared by the Editorial Committee of the American Rheumatism Association was the Eighth; it concerned the American and English literature for 1940 and was published in the Annals of Internal Medicine, Volume 15, December, 1941. This Ninth Review, begun in 1941, was interrupted by the war as most of the Committee entered military service. This Review has been prepared and published under difficulties. Regrettably it was impossible to include the literature of 1946 because the Quarterly Cumulative Index Medicus for 1946 had not yet appeared when the contents of this review had to be determined. The editorial comments express the opinions of the authors of the Review, the Editorial Committee, and are not necessarily those of the Association.

Definition of "Rheumatism" and the "Rheumatic Diseases"

Unsatisfactory as they are, the terms "rheumatism" and "rheumatic diseases" remain the best under which to group illnesses characterized by pain and stiffness of joints, muscles and related structures. In Europe "acute rheumatism" usually refers to rheumatic fever.[1215, 1831] Derivation of terminology was discussed by Edgecombe. An interesting historical note on "arthritis through the ages" was published by Burbank.

General Incidence of Rheumatic Diseases: Social and Economic Importance

The great responsibility of the medical profession and laymen to the problems of rheumatism was again emphasized in the Association's revised "Primer on arthritis."[362] In the United States, rheumatism heads the list of specified chronic diseases. Disability from rheumatic diseases exceeds that from tuberculosis by a ratio of 10:1, that from diabetes by nearly 10:1, that from cancer and tumor by 7:1. England and Wales have more than 1,000,000 adult sufferers from rheumatism yearly.[1215] Among 1,800,000 medically insured persons in Scotland, during a five-year period ending in 1938, rheumatism caused 3,000,000 days of incapacity and 45,300 new cases of disability, mostly certified as "muscular rheumatism." When "articular rheumatism" was present, the incapacity was prolonged.[1215]

American and foreign reports reveal a growing appreciation of the social and economic importance of rheumatism. In the United States rheumatism has annually invalided 147,000 persons, has cost 97,000,000 days lost from work, $200,000,000 in wages and more than $100,000,000 for medical care.[362, 1157]

In the British Isles, a sixth of the total absenteeism due to sickness is attributable to rheumatic diseases: "The time lost by reason of chronic rheumatism is equal to having an army of 60,000 people off work all the year round" (Underwood). "Chronic rheumatic joint disease" costs Great Britain 20,000,000 to 25,000,000 pounds annually.[523, 864] Rheumatism is one of the most important unsolved medical problems in the British Isles, according to Horder.[526c] In Scotland about 335,000 new cases of rheumatic disease are reported yearly. More than a fourth (27 per cent) of the prolonged absences from school were due to rheumatic diseases as compared to 7 per cent from tuberculosis. "There are at least 200,000 child sufferers from 'rheumatism' in the Kingdom" (Horder).[864]

In Sweden a twenty-fifth of the population suffers from rheumatic disease, according to a recent survey.[381] Of Sweden's population of 6,500,000 persons, 100,000 were permanently incapacitated despite the fact that arrangements for treating rheumatism in Sweden are probably the best in Europe. In Sweden 9 per cent of the total pensionable invalidity is due to rheumatism[1831]; between 40,000 and 50,000 persons received premature pensions in 1942 because of rheumatic diseases and there were 70,000 pensioned rheumatics.[1747]

According to Horder[866] the contingencies of war, which subjected civilians and military personnel to inclement weather, to manual labor to which many were unaccustomed, and to nutritional deficiencies and psychic shock, increased the incidence of rheumatism.

Classification of Diseases of Joints and Related Structures

If the etiology of the various rheumatic diseases were known, their classification would be simplified. Meanwhile some physicians merely consider rheumatism as articular or nonarticular, acute or chronic. Others divide the arthritides into (1) those of known etiology and (2) those of unknown etiology.[1157] Several classifications based on clinical features recently appeared.[173, 271, 504, 523, 570, 727, 740, 864, 1798, 1937] The inclusive classification recently prepared by the New York Rheumatism Association follows [1745]:

A. Infectional arthritis of proved etiology
B. Probably infectional; etiology unproved
   1. Arthritis of rheumatic fever
   2. Rheumatoid arthritis (atrophic, chronic infectious)
      (a) Adult type
      (b) Juvenile type (Still's disease)
      (c) Ankylosing spondylitis (Marie-Strümpell, etc.)
      (d) Psoriatic arthritis
   3. Arthritis associated with various infections
C. Degenerative joint disease
   1. Osteoarthritis (hypertrophic, degenerative)
      (a) Generalized
      (b) Localized
         (1) Secondary to previous trauma
         (2) Secondary to structural abnormality
         (3) Secondary to previous infectional arthritis
         (4) Cause unknown
D. Arthritis associated with disturbance of metabolism
   1. Gout
   2. Others
E. Arthritis of neuropathic origin
   1. Secondary to tabes dorsalis
   2. Secondary to syringomyelia
F. Neoplasms of joints: cyst, xanthoma, hemangioma, giant-celled tumors, synovioma
G. Mechanical derangements of joints
   1. Traumatic arthritis
   2. Joint disturbance secondary to abnormal postural strain
H. Miscellaneous forms
   1. Manifestations of systemic disease
      (a) Arthritis of serum sickness
      (b) Arthritis of hemophilia
      (c) Intermittent hydrarthrosis
      (d) Pulmonary osteo-arthropathy
      (e) Hysterical joints
   2. Local joint disturbances
      (a) Aseptic bone necrosis
         (1) Secondary to contusion, fracture, dislocation or air embolism
         (2) Of unknown etiology (juvenile osteochondritis, Legg-Calvé-Perthes' disease, Kohler's disease, Freiberg's disease, Osgood-Schlatter's disease)
      (b) Osteochondritis dissecans
      (c) Osteochondromatosis

Excellent criteria for diagnosis of these various types of arthritis are appended to this classification.

The 1942 "Primer on arthritis" [362] listed five main groups of arthritis: (1) proved infectious, (2) probably infectious, etiology unknown, (3) degenerative joint disease, (4) resulting from physical trauma, and (5) gouty arthritis.

The classification recently approved by the American Rheumatism Association for inclusion in the "Standard Nomenclature of Disease" follows:

1. Arthritis due to specific infection. *Specify organism when known.*
2. Arthritis due to rheumatic fever.
3. Arthritis, rheumatoid. *Specify as multiple or of spine.*
4. Degenerative joint disease, multiple due to unknown cause; osteoarthritis.
5. Arthritis due to direct trauma.
6. Arthritis due to gout.
7. Neurogenic arthropathy.
8. New growths of joints.
9. Hydrarthrosis, intermittent.
10. Periarticular fibrositis.
11. Diseases in which arthritis, arthropathy or arthralgia is frequently associated (diagnose disease, list joint manifestation as symptom):

Acromegaly
Acute disseminated lupus erythematosus
Cyst of meniscus of knee
Dermatomyositis
Drug intoxication. *Specify.*
Erythema multiforme exudativum
Erythema nodosum
Hemophilia
Hysteria
Ochronosis
Osteochondritis dissecans
Osteochondromatosis
Periarteritis nodosa
Psoriasis
Pulmonary osteo-arthropathy
Purpura, various types
Raynaud's disease
Reiter's disease
Scleroderma
Serum sickness

[For the sake of simplification, clarity and unification of terminology it is suggested that this classification of the American Rheumatism Association be adopted throughout the United States.—Ed.]

Relative Frequency of the Rheumatic Diseases

Among 48,000 people in Sweden, a recent survey showed 2.4 per cent had, or had had rheumatic fever; 2 per cent rheumatoid arthritis; 1 per cent osteoarthritis, and 2.6 per cent sciatica (Copeman).[381] [This was a small sample of the population; other forms of rheumatism were not mentioned, hence this survey may not have indicated accurately the relative incidence in Sweden.—Ed.] The distribution of different types of rheumatism among 1,000 civilian cases of "chronic rheumatic diseases" in London was determined by Fletcher and Lewis-Faning. There were 254 instances of "infective arthritis" [rheumatoid arthritis?—Ed.], 53 of "spondylitis ankylopoietica," 253 of osteoarthritis (not of spine), 44 of malum coxae senilis, 40 of gout, 114 of fibrositis, 10 of rheumatic fever and the remainder (232 cases) of miscellaneous types.

Interesting reports on types of rheumatic disease among soldiers in the recent war appeared. In a west coast United States Army General Hospital during 1942, 11 per cent of total admissions to the medical service were for rheumatic disease. Of 350

cases studied by Boland peripheral joints were affected in 214 (61 per cent); the remainder had "back complaints." Among the 214 patients with peripheral joints affected the relative incidences were as follows (in percentages): psychogenic rheumatism in 21; rheumatoid arthritis in 19; osteoarthritis in 16; acute rheumatic fever in 16; "arthritis unclassified" in 14; primary intramuscular or periarticular fibrositis in 5; gonorrheal arthritis in 2; gouty arthritis in 1 and miscellaneous articular conditions in 6. Later Boland and Corr at the same hospital found the relative incidence of "back complaints" among soldiers to be as follows (percentages): unstable backs 33; rheumatoid spondylitis 18; psychogenic rheumatism 18; spinal osteoarthritis 10; primary fibrositis 7; osteochondritis juvenilis dorsi 7; ruptured intervertebral disk 7.

The high incidence of psychogenic rheumatism in these series will be noted. In addition to the patients whose primary complaints were from psychogenic rheumatism, 13 per cent more had various organic rheumatic conditions with marked functional overlay—secondary psychogenic rheumatism.

The relative incidence among these American troops can be compared to that among 270 rheumatic British soldiers studied by Savage[1541]: 52 per cent had "fibrositis"; 15 postural backache; 9 sciatica; 9 osteoarthritis; 5 rheumatoid spondylitis; only 2 rheumatoid arthritis of peripheral joints; 1 rheumatic fever, and 7 per cent miscellaneous conditions.

Of the rheumatic diseases in a Scottish Army depot (World War II) 70 per cent were "muscular," 20 per cent "neuritic" and 10 per cent articular rheumatism.[1215] Among 775 rheumatic English soldiers in the Middle East (World War II) 33 per cent had muscular fibrositis, 32 per cent had acute arthritis, 21 per cent had chronic arthritis and 14 per cent had sciatic pain (Kersley).[989]

[In another series of rheumatic British soldiers studied by Copeman,[1h] 70 per cent had fibrositis, only 6 per cent had rheumatoid arthritis; psychogenic rheumatism was not mentioned as having been included or excluded. The supposed great frequency of "fibrositis," the relative rarity of rheumatoid arthritis and the infrequency or absence of primary psychogenic rheumatism among British troops is in sharp contrast to the relatively high incidence of *primary* psychogenic rheumatism and low incidence of fibrositis among American soldiers as reported not only by Boland but more recently by other American medical officers. These striking differences may be due, at least in part, to the fact that American medical officers who were trained in rheumatology set up diagnostic criteria whereby fibrositis and psychogenic rheumatism could be differentiated more confidently.[816] Whenever such a differentiation was not attempted most if not all of the cases of psychogenic rheumatism were probably catalogued as "fibrositis."—Ed.]

Diseases of Joints Related Primarily to Trauma

Types of Trauma. Joints can be damaged (1) by acute single injury or (2) by chronic injuries from minor, repeated trauma or microtrauma. "Microtrauma is the result of minute force applied internally or externally so that no lesion such as hemorrhage, exudation, destruction of cells or necrosis is immediately evident" (Duschak). The sensory response is below the threshold of perception or exceeds it only slightly. Acute injuries may produce lesions of ligaments or cartilage, symptoms of which are long delayed and the presence of which later produces chronic, sometimes progressive (secondary), traumatic arthritis.[121]

Lesions Produced by Acute Trauma. These may be varied and should not be lumped thoughtlessly under a single term, "traumatic arthritis." Ligaments or capsule may be stretched, lacerated or ruptured. Synovial membrane may escape injury or traumatic synovitis may develop. In knees menisci may be displaced, detached or torn. Articular cartilage may escape damage or may be

compressed, split or detached from subchondral bone. Juxta-articular bursae may be the main or only site of trouble. In severe injuries a joint may be dislocated or a bone fractured (Bennett).[121]

The knee is the commonest site of traumatic lesions because (1) it is a mechanically weak joint and (2) it, more than any other, is subject to "a multitude of severe or trivial injuries." [1180]

Traumatic Synovitis. Although injuries rarely affect synovia alone, a direct blow or contusion occasionally produces "simple traumatic synovitis," generally with hemorrhagic effusion.[1180] In mild cases compression bandages and restricted activities are all that are required. Cold compresses are preferred to hot applications.[66] Recovery is complete in two or three weeks. Aspirations may be required when hemorrhagic effusions are marked. If synovitis becomes recurrent, suspect internal derangement.[66] In four cases of traumatic hydrarthrosis Pelner [1361] "reduced rapidly" the effusions by the oral use of ammonium chloride and a low salt, acid-producing diet. [The number of patients treated is too small to permit conclusions concerning such treatment.—Ed.]

Hemarthrosis. In joints severely injured hemarthrosis usually occurs and was present in 93 per cent of Mauck's 416 cases of injured knees. When swelling occurs immediately after trauma, it is almost always due to hemarthrosis. But hemorrhage into joints may occur without severe trauma.[66, 1359] In any event articular distention from such effusions (especially into knees) is a prime factor in preventing healing of ligaments and cartilage, and is one of the greatest factors in producing an unstable joint, hypermobile cartilages and subsequent locking and damage.[1180]

Lipohemarthrosis. Hemorrhagic fluid is roentgenographically homogeneous. If free fat is also present, the fluid is not of homogeneous density but tends to separate into layers. In eight cases of injury to knees Peirce and Eaglesham noted in lateral roentgenograms "fluid levels of differential roentgenographic density" providing evidence of injury to juxta-articular fat, particularly in subpatellar fat pad and at the base of cruciate spines. Juxta-articular fat, even the subpatellar fat pad, is outside the synovial membrane although it is within the joint capsule. Therefore, when "traumatic lipohemarthrosis" is present one may assume that, due to severe injury, fat has been extravasated from one or more of the fat depots and also that the synovial lining has been torn. [Roentgenographic changes described in this interesting paper were quite clear. This report confirms that of Holmgren (1942).—Ed.]

Acute Traumatic Arthritis. In less severe cases pain, tenderness and effusion may disappear soon with healing and no residues. Sometimes articular hyaline cartilage is damaged but produces no early signs or symptoms because it is avascular and has no nerve supply. Due to its limited regenerative capacity cartilage heals slowly. Repeated roentgenographic examinations help to determine whether a progressive articular lesion has resulted from the initial trauma (Bennett).[121]

Late (Secondary) Traumatic Osteoarthritis. When articular cartilage is cracked or its surface damaged sufficiently to cause a scar, reaction about this damaged site from repeated motion and use in time may produce enough excess osteoid and scar tissue to make the joint function abnormally with the eventual production of late secondary traumatic osteoarthritis. In the hip the round ligament especially may gradually become scarred and enlarged; the excess tissue initiates maladjustment of articular surfaces which, if long continuing, produces hypertrophic changes (Ghormley).[639]

In knees, unhealed intrinsic lesions commonly produce such late osteoarthritis; degeneration of articular cartilage is hastened by overweight, overuse or the continued presence of loose bodies (Moorhead and Lyall).

In shoulders of professional baseball pitchers osseous deposits "strikingly similar to osteoarthritis" often develop on the posterior inferior border of the glenoid fossa. These exostoses irritate the circumflex nerve and pain is referred to the deltoid region. Such lesions in the posterior part of the shoulder are those which (in contrast to the less disabling lesions of the anterior part) may shorten a pitcher's career. A special roentgenographic technic to reveal the exostoses and the surgical procedure for their removal was described by Bennett[123] who also discussed occupational osteoarthritis and osteochondritis in elbows of pitchers. Surgical removal of loose bodies often relieved symptoms and restored full function.

The continued use of pneumatic tools for drilling and so forth occasionally produces unilateral sequelae: in wrists osteophytes at head of radius and at first carpometacarpal joint, osteochondritis dissecans especially of lunate or navicular bone, "spiking" of os trapezium, small areas of osseous decalcification; in elbows osteoarthritis, osteochondritis or periosteal proliferation ("olecranon spurs"); rarely in upper part of arm, myositis ossificans, or osteoarthritis of shoulder joint and calcific bursitis or both (Copeman).[374]

The superimposed weight of a normal man weighing 75 kg. (165 pounds) while standing or walking does not affect bone but does affect compressible soft interposed parts (articular cartilages, menisci, intervertebral disks). When weight rests on one leg the tibial condyle bears, according to Duschak, about 90 per cent of the body weight, in this case about 70 kg., a pressure of about 2 kg. per square centimeter of articular surface or 2 atmospheres of pressure. This is nearly 12 times that exerted by the normal systolic blood pressure (only 0.17 kg. per square centimeter). Thus, as long as body weight rests on the leg the circulation of tissue fluid within avascular cartilage stops completely (circulatory intermission, "rheopause"). Since this rheopause is normally short, cartilage remains unharmed under physiologic conditions. During weight-bearing a hip bears about 40 kg., the pressure being 1.55 kg. per square centimeter or nine times the blood pressure. Intervertebral disks below and above the fifth lumbar vertebra bear about half the bodily weight or 35 kg., 1.4 kg. per square centimeter or eight times the blood pressure. The disk below the fourth cervical vertebra bears 4 kg., 1 kg. of pressure per square centimeter or six times the blood pressure.

Under normal conditions no disordered local metabolism arises but during prolonged standing as in certain occupations the local circulatory intermission is lengthened; the flow of tissue fluids stops for a longer period. Despite its low metabolism articular cartilage is damageable. When rheopause exceeds a certain duration, an automatic defense in the form of "corrective unrest" occurs (unpleasant pressures, unrest, slight pains and stiffness) which forces a change of position. "Prolonged rheopause means malnutrition of cartilage, accumulation of waste products and stimulation of new formation of functionally inferior connective tissue with reduction of elastic fibers (fibrillation)."

Premature degenerative osteoarthritis may result especially in policemen, soldiers, salesmen, cooks, waiters, factory workers, housewives, nurses, dentists, surgeons and others whose occupations require long standing. Measures to prevent or lessen the results of such static microtrauma include shortening of the rheopause by brief interruptions of weight-bearing, by intercalated suitable motions or exercises, active hyperemia to improve blood supply, reduction of venous congestion by exercises, massage, elastic bandages and treatment of varicose veins and correction of obesity and static deformities (pronated feet, knock knees, bow legs, kyphosis) (Duschak).

Osteoarthritis of Temporomandibular Joint. This may result from acute or chronic exogenous trauma or from increased laxity of ligaments and resultant chronic mild subluxation.[96, 289, 1203, 1558, 1588, 1600, 1848, 1931] Symptoms in one case

were relieved by surgical excision of the condylar tip.[1203] A new "simple and safe" treatment was used in 180 cases by Schultz and Shriner: repeated intra-articular injections of a sclerosing solution (sodium psylliate). The resulting mild fibrosis reportedly relieved symptoms in most cases.

Osteoarthritis of Patella. This may be associated with intrinsic lesions within the knee joint or may result from direct injury to the patella. The patella may become fixed to femoral condyles with marked limitations of motion. Patellar cartilage may become degenerated with the formation of a "squeaky knee." An offending patella may gouge deep grooves on the femoral surface. Secondary osteoarthritis of knee joint may ensue. In a few cases patellectomy was performed [66, 1261, 1981] with relief of pain and increased mobility of knee.

Internal Derangements of Knee. Various internal derangements including those encountered by soldiers [1000] and by football players [1337] were discussed.

According to Mauck the primary damage is usually to ligamentous structures; medial collateral and crucial ligaments are most often damaged. Damage to semilunar cartilages is secondary. The more vulnerable medial meniscus is injured more often than the lateral.

The term "locking" received different interpretations. According to Levinthal [1083] "by locking we do not mean complete immobility." But Moorhead and Lyall [1261] wrote: "Locking is often used to describe difficult extension of the knee due to pain, whereas actually it should mean an insurmountable wedging of the joint. This is a very important distinction."

All internal derangements are accompanied by a varying degree of synovial hyperemia and effusion. If the irritating body is not removed, this membrane becomes permanently thickened and irregular with the late formation of hypertrophic or villous synovitis.[1261] Four cases of traumatic semimembranosus bursitis with tear of an internal meniscus, "an association not recorded in the literature," were noted by Burman.

The value of pneumoradiography (air arthrography) in the diagnosis of internal derangements was stressed and new technics were described.[161, 298, 414, 765, 795, 1675] Thus, calcified menisci were differentiated from calcified loose bodies or calcified articular cartilage.

The usual remedies were discussed.[66, 1000, 1083, 1180, 1261, 1337] A new plastic and steel knee brace weighing only 18 ounces (0.55 kg.) was demonstrated (Palmer).[1337] Conservative treatment should be employed first (temporary splinting, early weight-bearing, quadriceps exercises). When such measures fail surgical treatment is indicated, but should be done before irreversible secondary articular damage has occurred.

Sprains and Strains. The use of local anesthetics for sprains and strains was recommended. Often the part is "immediately restored to function" (Leinwand). Some used 2 per cent procaine hydrochloride.[1076] Others considered surface anesthesia by procaine iontophoresis as effective and more advantageous than the use of ethyl chloride spray [400, 1034] or injection of procaine.[1657]

Epicondylitis: Traumatic Radiohumeral Synovitis ("Tennis Elbow"). The terms "epicondylitis" and "tennis elbow" are inadequate and misleading because the condition is noted not only in sports but in industrial injuries (Allen).[18] Part of the disability results from nipping of the synovia of the radiohumeral joint. In obstinate cases the enlarged synovial fringe should be excised.

Secondary Influence of Trauma on Articular Diseases

Many articular diseases not primarily related to trauma (for example, rheumatoid arthritis, gouty arthritis, primary idiopathic senile osteoarthritis, neuroarthropathies) are notably influenced or modified by trauma of various sorts. The interrelationships were discussed.[121, 1521]

Gonorrheal Arthritis and Gonorrheal "Rheumatism"

Incidence. Despite a high annual incidence of 1,000,000 or more cases of gonorrhea,[1092] that of gonorrheal arthritis has decreased markedly.

In the presulfonamide era arthritis complicated 1 to 5 per cent of cases of gonorrheal urethritis; in Germany during World War I it complicated 10 per cent of cases of gonorrhea.[759] Recently the incidence has fallen to between 0.1 and 0.3 per cent (Turner and Sternberg). In recent literature few reports dealt solely with gonorrheal arthritis. Harkness discussed 336 cases; Davis 16 more. Among many reports on gonorrhea only 70 additional cases of gonorrheal arthritis were mentioned in sufficient detail for independent appraisal, and since gonococci were usually not found in synovial fluid, most of the cases were of presumptive, not proved, gonorrheal arthritis.[162, 413, 478, 580, 754, 831, 928, 1069, 1146, 1249, 1545, 1656, 1717, 1790, 1846, 1847] A few other cases of "arthritis" with gonorrhea were mentioned without any clinical details or results of treatment.[147, 350, 703, 1788]

Clinical Data. Polyarthritis occurred in 83 per cent of Harkness' 336 cases of gonorrheal arthritis. The arthritis began an average of 43 days after the onset of urethritis. [This average seems to us unduly long. Could some of these cases have been, not of gonorrheal arthritis, but of "postgonorrheal rheumatoid arthritis"?—Ed.] Most often affected were knees (74 per cent), ankles (56 per cent), feet (32 per cent) and wrists (16 per cent). Talalgia (periostitis of os calcis) affected 6 per cent. Sternoclavicular joints were affected in 1.4 per cent, temporomandibular and intervertebral joints each in 0.6 per cent.

"Metastatic catarrhal conjunctivitis," different from gonococcal ophthalmia in that no gonococci were found in smears or cultures, was a complication in 10 per cent of Gabe's 100 cases of gonococcal arthritis from which, incidentally, "septuagenarians are not exempt."

Pathology and Roentgenography. No new data appeared.

Laboratory Data. Cultures of gonococci are the most reliable method of diagnosis.

Culture media recommended were Difco Proteose Peptone no. 3 Agar enriched with 2 per cent hemoglobin [1583] or with 12 per cent horse blood.[1788] Sugar fermentation tests may be used to confirm positive cultures. Three negative cultures within four weeks were considered a minimal criterion of cure.

Gonococcal fixation tests are of doubtful value [1787]; results were positive in 77 per cent of Harkness' 336 cases of gonorrheal arthritis. Such tests may remain positive for as long as 50 years after the initial genital infection and a condition diagnosed gonorrheal arthritis 10 to 20 years after gonorrhea is "invariably not gonococcic even though the gonococcal fixation reaction may be positive." [759] Skin tests are of uncertain value.[1787]

Differential Diagnosis. No new data appeared.

Treatment of Gonorrhea and Gonorrheal Arthritis in General

Until 1943 the treatment of choice for gonorrhea and its complications was sulfonamide therapy. In cases refractory to sulfonamides, fever therapy was combined with the use of sulfonamides. By 1943, due to the disappearance of sulfonamide-susceptible strains and the increased spread of sulfonamide-refractory strains of gonococci, the percentage of patients cured by sulfonamides had fallen from the original 70 or 95 per cent to somewhere between 30 and 75 per cent.[350, 413, 415, 1069, 1146, 1788, 1983] In a few cases gonorrheal arthritis was cured by promin,[580] sulfapyridine,[1847] sulfathiazole [1249] and neoprontosil.[449]

Fever therapy gave cures in 79 per cent of 1,843 collected cases of gonorrhea and its complications, but the mortality rate was 0.6 per cent (one death in every 171 cases).[185] In 82 to 100 per cent of cases sulfonamide-resistant gonorrhea was cured by combining fever therapy with the preliminary use of sulfonamides.[1656]

Penicillin for Gonorrhea

Since 1943 penicillin has become the treatment of choice. In 95 to 98 per cent of all cases a single course of sodium penicillin, given intramuscularly or intravenously, will cure uncomplicated gonorrhea, including the sulfa-resistant type.[162, 352, 413, 478, 829, 831, 928, 958, 1545, 1717, 1788, 1790, 1826, 1828, 1846] An adequate course comprised 20,000 units given every three hours for six doses. The few patients (2 to 5 per cent) who failed to respond to one course, practically always responded to a second. The method of Romansky (a single injection of 150,000 units of calcium penicillin in beeswax-peanut oil) was widely approved.[1788, 1846]

Penicillin for Gonorrheal Arthritis

In the literature on penicillin under review (1943 to 1945, inclusive) we found mention of only 71 cases of gonorrheal arthritis treated with penicillin. Of these 71 cases only four were of proved gonorrheal arthritis, that is, cases in which gonococci had been recovered from synovial exudate.[23, 831, 1107] The remaining 67 cases must be classified as presumptive gonorrheal arthritis. In most of these no articular cultures had been made; in a few, cultures of synovial fluid had been made but were negative. Practically none of the cases were reported in detail. They were merely spoken of as cases of "gonorrheal arthritis," "acute gonorrheal arthritis," "arthritis with gonorrhea," "subacute arthritis with gonorrheal urethritis" or "complicating arthritis." [162, 247, 413, 440, 451, 478, 534, 754, 928, 1054, 1220, 1221, 1241, 1279, 1330, 1375, 1453, 1484, 1545, 1717, 1719, 1746, 1790, 1846, 1883]

Assuming for the moment that all 71 were actually cases of gonorrheal arthritis, results of use of penicillin can be summarized briefly (table 1). Of the 68 acute cases four were of proved, 64 were of presumptive gonorrheal arthritis. Cure was attained in all of the proved cases, but in only 59 per cent of the presumptive cases. In two proved cases penicillin, given intravenously or subcutaneously was promptly effective. In the two other proved cases only partial improvement resulted from the intramuscular or intravenous administration of 160,000 units given within 48 to 60 hours, whereupon in each case penicillin was given intra-articularly once a day for three days (a total of 8,700 and 10,000 units respectively) with prompt cures.

Of the three patients with chronic presumptive gonorrheal arthritis two (no details) were not cured.[1054] One patient who had presumptive gonorrheal arthritis of more than three years' duration [Difficult to believe.—Ed.] was reported as being cured promptly.[1746]

TABLE I

Results from Penicillin for Gonorrheal Arthritis

Type	Total Cases	Cured		Not Cured	
		Cases	Per Cent	Cases	Per Cent
Acute:					
Proved*	4	4	100	—	—
Presumptive	64	38	59	26	41
Total acute	68	42	62	26	39
Chronic:					
Proved*	0	—	—	—	—
Presumptive	3	1	33	2	67
Acute and chronic (Proved and presumptive)	71	43	61	28	40

* Proved: gonococci cultured from synovial exudate.

Of the 68 patients with acute gonorrheal arthritis, proved or presumptive, 62 per cent were cured, 38 per cent were not. Of the total 71 cases, acute or chronic, proved or presumptive, cure was obtained in only 61 per cent. Results for those cured were described as "dramatic," "unequivocal within 48 hours," "striking," "excellent," "immediate," "complete and rapid within a few days."

Reasons for Failure of Penicillin. If penicillin cures 90 to 98 per cent of all patients who have genital gonorrhea and its nonarticular complications why does it cure only about 61 per cent of patients who have gonorrheal arthritis? Why did it fail to cure 28 of the 71 patients? Several reasons have been advanced as possible causes for these failures.

1. Inadequate Dosage. Some failures admittedly resulted from the use of total doses (between 60,000 and 100,000 Oxford units) now known to be sometimes inadequate. No future failures should be properly attributed to inadequate doses.

2. Supposedly Inadequate Concentrations of Penicillin in Synovial Fluid. Certain failures have been explained by the curious notion that penicillin, given intramuscularly or intravenously does not get into the articular cavity in sufficient concentrations to cure gonorrheal arthritis. But penicillin in doses of 25,000 to 40,000 units given intramuscularly or intravenously every three hours, does penetrate rapidly into synovial fluid and attains concentrations comparable with those in serum (Balboni, Shapiro and Kydd; Rammelkamp and Keefer). In any event gonorrheal arthritis is not a disease of the articular cavity but of synovial and periarticular tissues. Since these tissues are highly vascular, even more so when inflamed, there is no reason to suppose that penicillin entering vessels of articular tissues should not reach infected regions.

3. Penicillin-Resistant Gonococci. Although certain bacteria have been made resistant in vitro to penicillin,[56] development of clinical resistance has not become a problem. Such an eventuality may be prevented, in part, by the use of adequate, not minimal, doses of penicillin.

4. Tardiness in Treatment. This may have accounted for certain failures as several of the patients had previously been treated unsuccessfully with sulfonamides.

5. Ineffective Penicillin. For a few months in 1945 commercial penicillin contained inordinate amounts of the relatively ineffective penicillin K. Ineffective

penicillin cannot be blamed for future failures as commercial preparations now contain a preponderance of potent penicillin G.

6. Errors in Diagnosis. The most common cause of past and future "failures" from penicillin has probably been and will be error in diagnosis. Experiences at an Army Rheumatism Center revealed that most cases of so-called gonorrheal arthritis resistant to penicillin were not of gonorrheal arthritis at all but were cases of rheumatoid arthritis in men who also happened to have gonorrhea, or of rheumatoid arthritis precipitated, reactivated or aggravated by genital (not articular) gonorrhea (Hench and Boland). This was shown by negative responses to therapeutic tests with high doses of penicillin (sometimes also sulfonamides or fever therapy), by the frequent involvement of new articular sites during treatment, by the subsequent course and slow development of symmetric fusiform polyarthritis as characteristic of rheumatoid arthritis, and in some cases by articular biopsies which revealed changes characteristic of rheumatoid arthritis, unlike those usually seen in acute or subacute gonorrheal arthritis.

Thus acute genital gonorrhea is just one more acute infection which, like tonsillitis, influenza, scarlet fever and others, can act as a trigger mechanism for the production of rheumatoid arthritis. Acute gonorrhea can provoke the first appearance of rheumatoid arthritis, reactivate previously active but currently quiescent rheumatoid arthritis, or aggravate notably a coexistent rheumatoid arthritis. Thus it would appear that "post gonorrheal rheumatoid arthritis" is now more common than gonorrheal arthritis.

Recommended Dosage of Penicillin. Penicillin should be given intramuscularly in doses of 25,000 to 30,000 units every three hours for seven to 10 days. If noticeable improvement does not occur within three or four days, intra-articular injections of penicillin of at least 10,000 to 20,000 units should be made once daily in joints large enough to be so treated (Herrell).[830] [If the intramuscular doses are large, intra-articular doses probably will be unnecessary.—Ed.]

Hypersensitivity to Penicillin Resembling Serum Sickness. No serious toxicity to sodium penicillin has been noted. The calcium salt also is nontoxic and more stable.[831] But recently reported were several cases of delayed sensitivity to penicillin, resembling serum sickness (see "Pharmaceutic Arthritis").

Tuberculous Arthritis

Incidence. Of 4,252 tuberculous patients 160 (3.8 per cent) had tuberculosis of bones, joints or both (Rosencrantz, Piscitelli and Bost).

Clinical Data. Physicians are tempted to regard a tuberculous joint as localized arthritis. "A tuberculous joint is always a local manifestation of a systemic disease." One should automatically search for tuberculosis elsewhere in the body.[314, 777, 1062] Pulmonary tuberculosis was associated in 42 to 74 per cent of recent cases of bone and joint tuberculosis [777, 1290, 1505]; and genitourinary tuberculosis in more than 20 per cent of one group.[1505]

New clinical, roentgenologic and statistical studies appeared.[777, 1057, 1093, 1290, 1505] One hundred patients, aged one to 16 years, were compared to 100 adult patients; pulmonary lesions were present in 42 per cent of the former, in 55 per cent of the adults (Nathanson and Cohen).[1290] More than one articular or osseous region was affected in 28 per cent of the 100 adults and 35 per cent of the children; as many as seven regions were affected in a single patient. In eight of the 160 patients of Rosencrantz,

Piscitelli and Bost [1505] one joint was considered the sole focus, no other tuberculous lesions being found.

[In statistical studies tuberculous lesions of joints are too often grouped inseparably with those of bones; hence, precise statistics on tuberculous arthritis are sometimes not obtainable.—Ed.]

Diagnosis. Diagnosis of tuberculous lesions of spine and joints should not be attempted from roentgenograms alone. Formation of bone does not always indicate secondary infection.[134, 1290, 1380] Features supposedly "characteristic" of tuberculous arthritis may be absent. Roentgenograms in lymphatic leukemia, septic arthritis and so forth, may simulate those in tuberculous arthritis.[1093]

Biopsy of regional lymph nodes was considered of diagnostic value.[635, 1894] Such biopsies were positive in 15 (94 per cent) of Gellman's [635] 16 cases of proved tuberculosis of bones or joints. The technic is simple and harmless; there are no contraindications. When conservative treatment is planned such biopsy is preferable to articular biopsy. It often can be done when a patient is "afraid to have a joint opened." But Webster warned against incautious interpretations of such biopsy material. Tuberculous inguinal adenitis was found in six of seven cases of tuberculous knees, in two of six cases of probable tuberculous hips, and in an adult with a tuberculous ankle. But in two cases of tuberculosis of the hips the inguinal adenitis appeared to have resulted from cutaneous tuberculosis rather than from tuberculous hips. A positive finding was of value; a negative biopsy was merely "inconclusive." [We prefer articular biopsies.—Ed.]

Special Localization: Clinical Data and Treatment. Tuberculosis affects chiefly weight-bearing joints, especially spine and hips.[1505]

1. Spine. This was affected in 41 per cent of one series [1057]; in 33 per cent of another.[1505] The upper thoracic vertebrae are more often affected in children; the lower thoracic in adults. Vertebrae may be attacked primarily in the anterior, central or posterior portions as well as at margins. Marginal involvement occurs most often in adults.[1290] In Pott's disease caseation of bone and soft tissue occurs first, then bony sclerosis. The latter is a vascular phenomenon resulting from loss of blood supply from thrombosis or endarteritis, or from occlusion or destruction of blood vessels by dissecting abscesses, according to Cleveland and Bosworth. In cases of tuberculous spondylitis, paravertebral abscesses may rupture into pleura or lung,[218] into mediastinum [1668] or into dura causing the Brown-Séquard syndrome.[75]

New roentgenographic studies stressed the following: Roentgenograms often fail to reveal spinal tuberculosis; they never reveal the full damage.[326] Bridging of vertebrae in spinal tuberculosis, formerly considered indicative of secondary pyogenic infection, probably is a reaction to irritation with periosteal formation of new bone or ligamentous ossification; it is not a healing process.[1380] Serial roentgenograms reveal first a thin disk (of early diagnostic importance), then a thinner disk with adjacent vertebral caries; finally disappearance of the disk, advanced caries and collapse of vertebral bodies.[776] Spinal pain intensified by movement, weight-bearing and jolting, relieved by rest, early evidence of thinned disk and isolation of tubercle bacilli from aspirated pus are points in early diagnosis.

Principles and results of treatment were discussed.[11, 13, 191, 313, 1006, 1062] Comparing three different technics in the surgical treatment in 123 cases, Bosworth and Haines found no advantage in using extra bone from tibia. Child preferred conservative, nonsurgical treatment in juvenile spondylitis.

2. Hips. Differentiation in children is simplified if one remembers that the common age of onset of tuberculosis of hips is one to five years, of Perthes' disease

between five and 10 years and of slipped femoral epiphysis between 10 and 15 years of age (Cholmeley). The roentgenographic localization of cavities and tuberculous foci in hips was discussed.[1063] In early tuberculosis of hips and in septic arthritis of hips but not in other conditions, the intrapelvic shadow cast in roentgenograms by the obturator internus muscle becomes obscured or widened; such a "positive obturator sign" is of diagnostic importance.[808]

Results from arthrodesis were reported.[314, 370] Roth [1510] considered fusion contraindicated in children less than six years old and "relatively contraindicated" in those between six and nine years old.

3. Greater Trochanter and Bursa. Trochanteric bursitis is often secondary to tuberculosis of the greater trochanter.[477]

4. Sacroiliacs. For early diagnosis the "Nachlas knee flexion test" was recommended.[1008]

5. Knee. Tuberculosis of knees may long, sometimes permanently, remain confined to synovia and not invade adjacent bone. In such cases roentgenograms are valueless for early diagnosis.[1342] If involvement of bone can be avoided, full motion may be obtained in 30 per cent of cases.[1062] In cases of chronic monarticular synovitis with synovial thickening and periarticular infiltration but no effusion, suspect "potential tuberculous infection" until the contrary is proved (Langston).[1062]

[This old axiom used to be statistically correct and useful, but tuberculosis of joints is now so (relatively) rare that a case of chronic monarthritis nowadays is much more likely to represent atypical monarticular rheumatoid arthritis than tuberculous monarthritis.—Ed.]

Extra-articular arthrodesis gave results satisfactory to King and Richards [1001] but is not applicable to children as it may arrest growth. Nonsurgical immobilization was recommended for children.[1062]

6. Other Joints. Shoulders are affected in less than 1 per cent of cases of bone and joint tuberculosis.[1062] Extra-articular fusion of tuberculous shoulders was successful after conservative or intra-articular fusion failed (Murphy and Wood).[1277]

General Remarks on Treatment and Prognosis. Attempts to treat the local lesion and ignore the general infection are doomed to partial or total failure. The proper employment of rest is the greatest single therapeutic factor. Once a joint is infected, recurrence of disease is likely unless treatment has restored full motion or provided firm ankylosis.[370, 777, 1057, 1062] In general surgical treatment is superior to nonsurgical. Of 118 patients treated conservatively (rest, immobilization) 16 per cent became well; 16 per cent improved; 14 per cent were unimproved; and 54 per cent died. Of 85 patients treated surgically 19 per cent became well; 27 per cent improved; 9 per cent were unimproved; and 45 per cent died (Rosencrantz, Piscitelli and Bost [1505]).

[The use of streptomycin may improve this gloomy picture. Preliminary results are encouraging.[850] Early tuberculous lesions confined to synovia may heal. As currently used, streptomycin will not replace operations for advanced destructive lesions.—Ed.]

"Tuberculous Rheumatism" (Poncet's Disease) and Nondestructive Tuberculous Polyarthritis

The concept that tuberculosis can produce not only the characteristic, accepted type of tuberculous arthritis (a destructive monarthritis or oligoarthritis with invasion by tubercle bacilli and tubercles) but also an acute polyarthritis resembling rheumatic fever or a chronic nondestructive polyarthritis resembling rheumatoid arthritis was introduced by Grocco (1892), publicized by Poncet (1902),

and more recently endorsed vigorously by Reitter and Loewenstein (1933) and others.[1c, 1d] This "tuberculous rheumatism" presumably results from the invasion of joints by tuberculous toxins from distant foci; hence, tubercles and tubercle bacilli are not found in affected articular tissues. This concept has found practically no support in the United States (Brav and Hench, 1934[1b]).

In 1938 Reitter and Loewenstein claimed to have recovered tubercle bacilli from the blood in a variety of conditions including different types of acute and chronic arthritis. This work found few supporters.[1119] Loewenstein again claimed to have found tubercle bacilli in blood and synovial fluid of patients during life and from blood, heart, spleen and tonsils at necropsy in cases of rheumatic fever, endocarditis and chorea. In certain cases of untreated rheumatic fever miliary tuberculosis has developed. Sensitivity to tuberculin changes from anergy in early rheumatic fever to hypoergy during convalescence. According to Loewenstein[1119] recurrent attacks of rheumatic fever result from endogenous or exogenous reinfection; superimposed infections may mobilize "sleeping foci" of tubercle bacilli; the clinical and anatomic features may be allergic.

Two critical observers, denying much of Poncet's theory and unable to accept the claims of Loewenstein have, nevertheless, presented two cases in partial support of the original thesis.

Montuschi presented the following case: Bilateral pleural effusion developed in a young man and lasted for several months; then acute febrile polyarthritis occurred; it disappeared after three weeks. The tuberculin test was strongly positive although tubercle bacilli were never found in sputum and roentgenograms of chest revealed indefinite findings. For reasons stated a presumptive diagnosis of tuberculous rheumatism was made.

A case with more definite findings was reported by Kling and Levine as one of nondestructive tuberculous polyarthritis (not "tuberculous rheumatism"). As a child, the patient had lived with tuberculous relatives. At the age of 25 years she had active pulmonary tuberculosis. At age 28 years when the roentgenogram revealed *no* active pulmonary disease, chronic arthritis of a knee and subacute recurrent arthritis and arthralgia in several other joints developed. The condition was called "rheumatoid arthritis" in the United States, "benign tuberculous rheumatism, Poncet type" when she went to Europe. At age 35 years fluid aspirated from a knee was negative on guinea pig test. Synovectomy was done; objectively the articular inflammation resembled a nonspecific, nondestructive synovitis but, surprisingly, synovia contained miliary tubercles; a few bacilli were found by staining; a guinea pig inoculated with macerated synovia developed glandular and visceral tuberculosis in six weeks. Kling and Levine concluded: Mild tuberculous nondestructive polyarthritis does occur as a hematogenous infection of joints from a visceral focus in a person with high tissue resistance. No diffusible tuberculous toxins have been identified. "It is not proved that the tubercle bacillus or its products are able to produce other than specific pathologic changes."

[An interesting, thought-provoking case which indicates that tuberculous arthritis may be polyarticular and of relatively nonspecific *clinical* type. But this case is one of tuberculous polyarthritis and does *not* support the concept of "tuberculous rheumatism."—Ed.]

Osteitis Tuberculosa Multiplex Cystoides

This represents sarcoidosis of bone and will be discussed under "Miscellaneous Conditions: Sarcoidosis."

Pneumococcal Arthritis

The incidence of arthritis as a complication of pneumonia is about 0.3 per cent. Primary or "cryptogenic" pneumococcal arthritis may occur without pneumonia (Blankenhorn and Grupen; Bogers [166]). There is no evidence that specific arthrotropic pneumococci exist. Although any joint may be involved, usually only one or two large ones are affected. Clinical features are like those of other acute specific pyogenic arthritides. Therapy with type specific Pneumococcus serum was successful [154] but sulfonamides are the drug of choice. Supplementary intra-articular instillation of sulfathiazole or sulfadiazine was considered of value.[166, 353] Penicillin should be equally efficacious. Combined with specific therapy, repeated joint aspirations were preferred to arthrotomy.[154, 166] Prognosis in the primary type of arthritis, formerly considered grave, appears to be excellent but prognosis in the secondary type depends on the severity of the focus of infection or bacteremia. Slight, if any, residual articular damage is to be expected if prompt and adequate therapy is instituted. An unusual case was reported in which spontaneous recurrence of suppuration occurred months after apparent healing.[353]

Syphilitic Arthritis and Synovitis

Articular disorders due to congenital or acquired syphilis were tabulated and discussed (Comroe [363]; Steindler). Of 2,400 syphilitic patients 119 (5 per cent) had skeletal lesions and 63 of these 119 had articular lesions: 22 had synovitis (nine associated with congenital, 13 with acquired, syphilis), 43 had Charcot's joints and five prepatellar bursitis from acquired syphilis.[237, 238] Wassermann tests on synovial fluid were positive in six of the nine cases of congenital syphilis and synovitis, in 10 of 11 tested cases of synovitis and acquired syphilis, in five of seven tested cases of tabetic joints.

In early congenital syphilis articular lesions are rare and leave no residual enlargement. In late congenital syphilis nongummatous articular lesions usually involve large joints and under treatment symptoms disappear. But gummatous articular lesions may produce synovitis, pannus, destruction of cartilage and residual damage.[1710] Syphilitic spondylitis with invasion of bone and periosteum by *Treponema pallidum* has a predilection for the cervical region; it is not to be confused with Charcot's spine. Six cases were reported, one of which was verified at necropsy (Freedman and Meachan [594]; Sgalitzer). On clinical and roentgenologic grounds syphilitic spondylitis can be distinguished from tuberculous, rheumatoid or osteoarthritic spondylitis. Syphilis of a biceps tendon and olecranon bursa with *Treponema pallidum* in granulation tissue was noted (Schrager [1556]). Juxta-articular nodules (subcutaneous fibroid syphilomas), rare lesions of late syphilis, have a predilection for elbows and knees and must be differentiated from the nodules of rheumatoid arthritis, gout, tuberculosis, xanthoma and various tumors.[941, 1304, 1827]

[The reported incidence of syphilitic arthritis or synovitis is falling notably as more exact diagnostic criteria are used. Many articular lesions, once considered syphilitic, are no longer so regarded. In our experience articular lesions of syphilis are much rarer than even current literature suggests. We agree with others [238] that the mere presence of an articular lesion or a positive Wassermann reaction of synovial fluid of a syphilitic does not necessarily indicate that the joint is syphilitic; most of them are not. The best diagnostic test aside from articular biopsy is a rapid response to antisyphilitic therapy; even this is not infallible.—Ed.]

Tabetic and Nontabetic Neuroarthropathies: Charcot's Joints

Typical Charcot's joints occur not only in tabes dorsalis but also in certain neurologic conditions: syringomyelia; tumors and injuries of spinal cord; spina bifida with involvement of nerves; neuritis or injury of peripheral nerves; leprosy and so forth.[204, 1374, 1400, 1711, 1817, 1956]

Tabetic Arthropathy. Charcot's joints develop in 5 to 10 per cent of cases of tabes.[1400, 1711] Often the joint symptoms first call attention to the underlying disease of the nervous system. Spinal fluid and serologic tests on blood for syphilis may give negative results in 50 per cent, but history and neurologic findings confirm the diagnosis. Usually one major weight-bearing joint is affected, but multiple joints may be involved.[1711]

In a study of 58 cases by Pomeranz and Rothberg joints affected were (in percentages): knee 38; tarsal 19; hip 18; ankle 8; spine 6; toes 4; shoulder 4; pelvis 3. More than one joint was affected in 32 per cent and symmetrical joints in 20 per cent. Clinical and statistical analyses of 214 Charcot's joints in 134 patients were made by Steindler, Williams and Puig-Guri. Cases of involvement of hip,[1960] knee[1066] and metatarsophalangeal joints of big toes[1533] were reported: in one case serial roentgenograms showed the progression in a hip in one year.[1960] Charcot's joint presents "an exaggerated form of osteoarthritis" (King[1002]); differentiation of tabetic hip from osteoarthritic hip was discussed.[971]

The pathogenesis of this articular disease is incompletely understood. Charcot stated that the changes were trophic in origin as a result of disease of the anterior horn cells or degeneration of peripheral nerves. But currently accepted[1711] was the concept of Eloesser (1917) who found that bone and joint changes corresponding to those in Charcot's joints could only be produced in animals by cutting the posterior nerve roots and then subjecting joints to trauma; in the absence of trauma, no arthritis developed. This agrees with observations in man that acute trauma frequently (40 per cent of cases) precedes the development of a Charcot joint.[1711] Pain may be a manifestation of a Charcot joint. It occurred to some degree in 56 of the 58 cases of Pomeranz and Rothberg.

Syringomyelic Arthropathy. In about 25 per cent of cases of syringomyelia Charcot's joints, arthropathies locally indistinguishable from tabetic joints, develop. But tabes affects upper extremities much less frequently than does syringomyelia.[1400, 1711] A case of syringomyelia was studied with serial roentgenograms: extensive destructive changes developed in a shoulder within seven weeks (Pendergrass, Gammon and Powell).

"Charcot Joints" (Unclassified). The synovial membrane in a Charcot joint (unclassified as to type, whether tabetic or otherwise) revealed retrogressive alterations (atrophy, degeneration, necrosis) but also progressive and proliferative changes and well-developed Golgi networks (King).[1002] Radiographically the following sequence of events occurred in Charcot's joints: hydrarthrosis, disintegration, hypertrophy, atrophy; these stages were illustrated.[204, 1817]

Treatment of Charcot's Joints. Current reports concerned tabetic joints chiefly. Treatment is unsatisfactory. Tabetic joints are not affected by antisyphilitic therapy. Conservative orthopedic treatment (nonsurgical immobilization) was recommended by some who considered attempts at surgical fusion often disappointing.[1400, 1711, 1956] Others favored surgical fusion.[997] A tabetic knee was thus successfully treated (Lapidus).[1066]

Yaws (Frambesia Tropica)

Yaws is a specific endemic tropical disease caused by the spirochete, *Treponema pertenue,* morphologically indistinguishable from *Treponema pallidum.* Because of this and because the manifestations of yaws are so like those of syphilis, some writers consider the two conditions identical. Others emphasize the distinctions: yaws is not a venereal disease; it rarely attacks viscera or central nervous system; but like syphilis it attacks bones and joints, the acute lesions of which were discussed by Helfet. Acute juxta-articular osseous lesions may simulate acute arthritis with pain, tenderness, swelling, spasm and limited motion. Joints and tendon sheaths may be chronically affected: a relatively painless progressive proliferative synovitis occurs, apparently without involvement of cartilage. A photomicrograph of affected synovial membrane was shown. Spinal involvement often results in ligamentous calcification, localized or diffuse, resembling ankylosing (rheumatoid) spondylitis. Tendinous ganglia often appear. Wassermann and Kahn reactions are invariably positive. Treatment with arsenicals reduces most symptoms rapidly; swelling slowly.

Brucellosis: Undulant (Malta) Fever

Incidence. Between 1930 and 1943, 36,513 cases were reported from the United States.[897] Some authors feared that the increasing prevalence and failure of recognition might present a serious problem.[296, 563, 772, 783, 1836] Others were less perturbed: exposure is fairly common, but the disease is subclinical and harmless in most cases (Goodman).[678]

Brucellosis is more common in rural communities but is common in all groups, particularly among laboratory workers, farmers, butchers, slaughterhouse employees and veterinarians.[772, 783] The method of transmission may be materially different in various areas. Cases from direct contact are more frequent than those from contaminated dairy products.

That children are less susceptible than adults [291, 1684] was doubted by Hagebusch and Frei who in three years saw 182 children with brucellosis; 95 per cent of them were less than six years of age. Maternal infection can be transmitted to the child in utero or during delivery.

Clinical Data. Brucellosis in the general population may be acute, chronic or latent and asymptomatic. The goat strain of Brucella produces the most violent effect in man, the porcine less severe and the bovine least severe.[854] The manifold clinical manifestations were reviewed.[446, 705, 783, 1150, 1684, 1685] Acute brucellosis is a clear-cut clinical entity [1835] but probably less than 10 per cent of patients with chronic brucellosis give a history of a previous acute attack.[854, 1088] Splenomegaly was the most consistent finding in acute infections; it was noted in 34 per cent of cases (Levitt).

Chronic brucellosis is difficult to recognize. Fever is not always present; it was absent in 23 per cent of cases (Griggs) [705]; when present, it seldom runs a wavelike course (Holbrook).[854] Suggestive features are fatigability, weakness, lethargy, headache, abdominal pain, constipation, colitis, pelvic disorders, menorrhagia,[446] nervousness and insomnia. In many cases a diagnosis of neurasthenia is made. Ocular, oral, pulmonary, cardiac and lymphatic manifestations were described with splenomegaly in 40 per cent of cases (Spink and Hall). The spleen may be greatly enlarged [1967]; sterility has occurred.[729]

Symptoms Referable to Muscles and Joints. Arthralgia and general aches in muscles, limbs and joints also were described.[705, 1088, 1150, 1619, 1684, 1685] In five

of 100 cases of chronic brucellosis destructive bone lesions were present (Griggs).[705] In one series of 48 cases "arthritic pains," including backache were found in only 8 per cent (Urschel).[1836] Periarthritis, bursitis and hydrarthrosis may be observed (Carpenter). Spondylitis probably is the most common articular or osseous complication of brucellosis[1386]; 68 cases of brucellar spondylitis, usually lumbosacral, have been recorded in the literature (Spink and Hall). Localization to the spinal region has occurred from three weeks to one year after the original infection.[1386] Five cases of destruction of lumbar vertebrae were reported.[472, 835, 1386, 1684]

Pain and stiffness of spine were usual symptoms. The lumbar and thoracic regions were most often affected. The picture was generally more acute but more benign than in tuberculosis. Formation of abscesses and deformity were rare as destructive changes were not extensive. Roentgenograms characteristically showed a zone of sclerosis spreading to involve the whole vertebrae. The disk was involved late.

As cases of brucellar spondylitis unlike the destructive cases just described Goldfain[664] reported five cases resembling rheumatoid (ankylosing) spondylitis, Marie-Strümpell type. Diagnosis was based on positive agglutination and skin tests and opsonic indexes.

[The case reports were meager. Roentgenographic changes were not described. It is probable that these patients had rheumatoid spondylitis and unrelated coincidental brucellosis.—Ed.]

Brucellosis must be considered in the differential diagnosis of all types of arthritis; when raw milk is used, a high percentage of "run-of-the-mill" cases of arthritis are associated with Brucella infection and respond to specific therapy, according to Harris. [We do not agree.—Ed.] The arthritis is likely to be atypical and joint involvement bizarre. Acute joint manifestations may resemble those of rheumatic fever.[772, 1819] Chronic brucellosis was considered by Goldfain[663, 664] to be the cause in two typical cases of rheumatoid arthritis.

Such reports prompted Green and Freyberg[695] to study the incidence of active brucellosis in patients with rheumatoid arthritis and other rheumatic disease. No brucellosis was found in 25 cases of typical rheumatoid arthritis. Of 25 patients with miscellaneous rheumatic disorders, three had active brucellosis, six had possible brucellosis. Green and Freyberg[695] concluded: "Arthralgia and other rheumatic symptoms are common in brucellosis, and *temporary* nonpurulent joint inflammation may occur, but brucellosis is seldom if ever the cause of *chronic* non-purulent joint inflammation."

[Many physicians in the Southwest have been led to "think first of brucellosis" in almost any case of chronic arthritis. But in our experience brucellosis is about the last thing to think of as the cause of chronic arthritis of the rheumatoid type.—Ed.]

Diagnosis. A long, searching history is the first requisite.[705] The diagnosis of brucellosis is established with certainty only by culture and identification of the organism from blood or tissue fluids[773, 1088, 1619, 1835, 1952] but, unfortunately, cultures are usually negative.[729, 772]

The inadequacy of the agglutination test was stressed by many,[705, 729, 772, 879, 1088, 1619] but Green and Freyberg[695] found it the most reliable of the common diagnostic procedures; others considered it the most sensitive test.[296] Conflicting reports

on the value of the skin test also appeared. Some believed it to be valuable [703, 772, 783]; others disagreed.[678, 1619] A positive test indicates only that the patient has been sensitized some time.[291] Urschel [1838] considered brucellergin the best antigen for routine skin tests.

[Intradermal skin tests may be very irritating; unless control tests are made an "irritation reaction" may be misinterpreted as a positive reaction. Skin tests made in active cases of brucellosis are not without danger; there is a 30 per cent chance of producing an Arthus phenomenon which may result in ulcer formation lasting weeks or months.—Ed.]

Most writers were skeptical of the value of the opsonocytophagic test,[291, 678, 695, 1684] but Harris [772] found it accurate in diagnosis and helpful in prognosis. The various tests must be correlated with the clinical picture. Animal inoculations may be of value.[291, 783] A provocative test with typhoid vaccine should constitute one of the diagnostic methods.[783] Sedimentation rates are increased in a small proportion of cases. Leukocyte counts may be low, normal or high.[705] The important factor is the presence of a relative or absolute lymphocytosis.[1684] Eosinophilia was noted.[525] The diagnosis of Brucella infection often has to be made by exclusion.[1835] [But many presumptive diagnoses of brucellosis are, in our opinion, inaccurate.—Ed.]

Treatment. No one method of treatment can be relied on in all cases.[772] Evaluation of remedies is difficult as most patients with early disease respond to rest in bed and symptomatic treatment. "Successful results" should often be attributed to the nature of the disease rather than to the agent used.[879]

1. Chemotherapy. After reviewing the literature on sulfonamides Urschel [1837] concluded that their use is not warranted in brucellosis.[95, 446, 854, 879, 1097] Many agreed, but others approved their use in acute cases.[729, 772, 1684] They are valuable only if they produce a severe drug reaction.[783] Treatment with sulfaguanidine and sulfasuxidine was satisfactory (Davis [447]; Sarvis). Strains of Brucella are resistant to penicillin in vitro (Spink). Penicillin was not effective in experimental brucellosis of guinea pigs.[1741]

2. Serums and Vaccines. Heat-killed Brucella vaccine was considered effective by some.[706, 772, 843, 1088] Equally good results were obtained with brucellin.[783, 1619] Brucellin was used in more than 3,000 cases but was not always successful according to Huddleson. Convalescent human blood or serum was considered useful in acute cases by some (Carpenter; Hartsock), but remissions may occur.[879] Foshay's serum was reported to have been "100 per cent effective" in acute cases of one to four months' duration.[729]

3. Fever Therapy. This was considered best in cases in which the disease was refractory to vaccine, and was thought to be useful in cases of localized infection or in cases of acute or subacute Brucella arthritis.[772, 773] It was reported as being effective in most cases of brucellosis, including three cases of Brucella spondylitis.[1886] It supposedly produced remission in 13 of 18 cases of brucellosis.[932, 933]

4. Other Treatment. Typhoid vaccine [772] given intravenously was of no value. In a preliminary note, Schreiner reported that five patients were treated successfully with radioactive colloidal manganese. A successful method of treatment still awaits development.[678] [There is as yet no specific treatment for brucellosis.—Ed.]

5. Prophylaxis. Protection may be afforded to humans by vaccine, but further studies are essential.[291, 1025, 1026, 1027, 1619, 1620]

Typhoid Arthritis

Monarticular, less commonly a polyarticular, arthritis is an occasional complication of typhoid fever. "Typhoid spine," an inflammatory lesion of vertebral

periosteum, is usually of low grade and tends to be chronic. Abscess formation rarely occurs. Lower thoracic and lumbar vertebrae are affected most commonly. Tenderness, muscle spasm, limited motion, scoliosis and kyphosis may occur. Usually only two contiguous vertebrae are affected. The intervertebral disk may be narrowed or absent; there is irregular density of the adjacent vertebral bodies. Perispinal ligamentous ossification is frequent and may lead to complete bony bridging of the two affected vertebrae. The diagnosis may be suspected from a history of backache during or after typhoid fever, either immediately or weeks later, and confirmed from the roentgenogram. The incidence of typhoid spondylitis is low; among a recent group of 410 typhoid patients only one had persistent backache considered to be from "typhoid spine" (McMaster). In an unusual case of typhoid spine, in which symptoms first appeared 12 years after, and suppuration 22 years after, typhoid fever, the abscess ruptured into a lung and a psoas abscess also formed (Johnson and James). Treatment of typhoid spine includes rest and immobilization with cast or back brace. In the absence of suppuration, complete recovery with good function is the rule. In severe cases spinal fusion may be indicated.[915, 1208]

Meningococcic Arthritis

"Since the identification of the meningococcus by Weichselbaum (1887) the clinical concept of meningococcal infection has been dominated by its most serious manifestation, meningitis," [467] but "from the practical standpoint it is vital to view the disease primarily as a septicaemia, the organism invading the blood stream from nasopharynx with localization in skin, joints, meninges, and other body tissues." [431] That meningococcemia without meningitis can no longer be considered a medical rarity is supported by new studies.[375, 431, 467, 846, 1153, 1639, 1738] In such cases a variety of diagnoses, chiefly rheumatic fever, influenza, arthritis and erythema nodosum, were reported on admission. Meningitis was not epidemic in the regions concerned.[375, 467]

Incidence of Articular Manifestations. The loose use of the term "arthritis" by many authors made calculation of the incidence difficult (Boger).[167] Arthritis was the most frequent disabling complication in one series of 100 patients: 11 had definite joint symptoms (arthralgia in four, suppurative arthritis in seven).[1738] Of 3,005 cases of cerebrospinal fever, arthritis was a complication in 2.7 per cent (Beeson and Westerman). Among 1,000 children with meningococcic infection reported from Chile, arthritis was diagnosed clinically in 3.7 per cent, but in 13 of 52 cases in which postmortem examination was performed, purulent synovitis which had not been diagnosed clinically was discovered (Bass and Nothman). Fox and Gilbert found the incidence of articular complications to have been 1.9 per cent before the use of sulfonamides and 11.8 per cent after the advent of chemotherapy, a discrepancy which "may well be accounted for by the lessened mortality with more opportunity for complications." Meningococcic arthritis was said to occur most often in children less than two years of age (Chont).

Clinical Data. The differentiation of two types of meningococcic arthritis by Herrick and Parkhurst in 1919 (type A, early transitory hemorrhagic polyarthritis; type B, a subsequent or independently occurring monarticular suppurative arthritis) was discussed.[167, 297, 582, 1738] A somewhat similar distinction was made by Bauer, Ropes and Short: one type of arthritis, usually symmetrical,

may occur early in the course of the disease with little swelling or effusion but with polyarticular pain and tenderness; another type with metastatic pyarthrosis generally occurs toward the end of the last week of disease and usually affects only one joint, commonly a knee.

What is generally referred to as "arthritis" is, in most cases, an acute synovitis which usually subsides promptly with complete restoration of joint function. In exceptional cases the synovitis leads to purulent arthritis with effusion (Boger).[167] Purulent arthritis was noted most frequently in knees but metacarpophalangeal joints, elbows, wrists, hips and ankles also were involved.[167, 297, 582, 954, 1153, 1738] In one patient, seven weeks of age, suppurative arthritis occurred in both hips during the second week of illness (Bass and Nothman).

Joint symptoms are not related to the objective severity of the articular disease.[582] Striking differences may occur: in one case the violence of the polyarthritis, with excruciating pain and swelling in many joints was outstanding; in a contrasting case of slight swelling in one knee, there was no pain on manipulation, no redness or tenderness although culture of synovial fluid revealed meningococci.[167] In another case [297] gentle passive motion of fingers or forearm elicited screaming, but there was no articular swelling, redness or heat. Swelling, crepitation, stiffness and pain on motion may persist after other signs of infection have disappeared.[1738]

Diagnosis may be confused by the coincidental presence of a positive gonococcic complement fixation test.[167, 954] Spectacular improvement in joint symptoms and fever on cessation of drug therapy led to a diagnosis of sulfadiazine arthritis in two of 134 patients given massive dosage (see "Pharmaceutic Arthritis").[1153]

Pathology and Laboratory Data. No noteworthy data on the pathologic changes in meningococcic arthritis have been added to those of Keefer, Parker and Myers.[1b] Meningococci were found in joint fluid in a third of the suppurative cases. The fluid was mucinous, serous, seropurulent or frankly purulent (Fox and Gilbert). Despite the presence of greenish or yellow purulent synovial fluid, cultures and smears of fluid were negative for meningococci in some,[297, 1738] positive in others.[82, 167] Cattell reported that in synovial fluid, leukocyte counts varied between 26,200 and 78,700 per 100 c.c. with 98 to 100 per cent polymorphonuclear leukocytes. Recovery of the organism from blood in nonfulminating cases was largely a matter of chance. Twenty-one samples of blood from one patient yielded only two positive cultures.[467] Mester's "specific" reaction was of no value in diagnosis (Copeman and Stewart). Roentgenograms made in one case after purulent arthritis had subsided were negative [582]; in others destruction, extensive demineralization and narrowing of joint space were noted.[167, 1738]

Treatment. Chemotherapy is the treatment of choice. But the occurrence or continuance of suppurative arthritis or both sometimes were noted even when concentrations of sulfonamide in the blood should have been adequate.[167, 297, 582, 1153, 1738] Possible reasons for such failures were given.[297, 582, 1738]

Massive doses of sulfadiazine were recommended by Marangoni and D'Agati who considered a concentration of 15 to 20 mg. per 100 c.c. of blood optimal, but the incidence of toxic manifestations was high (28 per cent). Initial intravenous therapy was advised in seven cases of fulminating disease. Among 112 soldiers with meningococcic infections those treated with small doses of sulfadiazine fared better than those given large doses.[431] A high degree of success, with a low complication rate, was attained by maintaining the concentration of sulfadiazine at 8 mg. per 100 c.c. of blood.

Strong and Hollander advocated intensive chemotherapy during the acute

stage of arthritis, aspiration of demonstrable effusion, immobilization of affected joints, and subsequent physiotherapy. According to Boger [167] purulent meningococcic arthritis should be treated conservatively: "The effusion frequently resolves spontaneously but large ones may call for repeated aspiration; arthrotomy seems to have no place; appropriate splinting may give great comfort." Two patients who did not respond rapidly to sulfadiazine were given polyvalent antimeningococcic serum intravenously and recovered.[431] Three patients with meningococcemia recovered without therapy.[1618] Factors other than therapy, such as the development of bactericidal powers in the patient's blood, are responsible for recovery from meningococcic infection.

Penicillin cured acute meningococcic arthritis in one case.[1375] [Opinions differ as to the drug of choice: some still favor sulfonamides; others believe that penicillin is generally preferable except in overwhelming infections in which case both penicillin and sulfonamides should be used.—Ed.]

Results and Prognosis. During World War I, complications and sequelae from meningococcic infections were relatively common; the mortality rate ranged from 30 to 50 per cent (Strong and Hollander). In contrast, recent reports revealed only two deaths in 100 cases,[1738] one in 112 cases,[431] four in 129 cases,[1153] nine in 51 cases.[1639]

"The prognosis of the acute synovitis is uniformly excellent but when the joint space is invaded the prognosis should be a little more guarded" according to Boger [167] whose review of 66 reported cases (not all proved) indicated that in 12 per cent permanent articular damage developed. In another group, more than half the patients with arthritis recovered completely (Beeson and Westerman).

Suppurative Arthritis

General Comment. Suppurative arthritis may result from neighboring bone disease, penetrating injury or metastatic infection. Multiple joints may be involved.[150, 574, 803] Persons less than 30 years of age are most often afflicted especially in hips and knees.[150, 803] The articular picture may be masked by the systemic reaction to suppuration.[150]

Of Streptococcic Origin. Streptococci were recovered from 45 of 150 joints cultured (Heberling). Goodyear reported polyarthritis due to *Streptococcus viridans* in an infant seven weeks old, supposedly secondary to dental focal infection in the mother. When streptococci are the causative bacteria, primary synovial infections usually result (Russo).

Of Staphylococcic Origin. Staphylococci were isolated in most cases of suppurative arthritis, since these bacteria are commonly responsible for osteomyelitis, the most frequent precursor of suppurative arthritis.[803]

Treatment. The necessity for early diagnosis (by joint aspiration and culture) and early treatment was stressed.[574] Initial sedation, establishment of fluid balance, immobilization and transfusions if indicated were advised. Arthrotomy continued to have its advocates [150, 325, 803]; a new operation for adequate drainage of the hip was described (Girdlestone). Suppuration was controlled by multiple aspirations combined with systemic sulfonamide therapy (Beach; Blaisdell and Harmon). Penicillin promptly cured septic arthritis due to *Staphylococcus aureus* in one case.[958] Key [906] recommended daily intramuscular and intra-articular injections of penicillin supplemented by arthrotomy if destruction of

cartilage has occurred. [Early judicious use of chemotherapy, antibiotics and frequent aspirations of joints may prevent many arthrotomies in the future.—Ed.] Immobilization of joints by traction or plaster and also the early use of active motion were generally advised (Heberling). [With fewer arthrotomies necessary, perhaps active motion can be instituted earlier while joints are still in traction, with the hope of obtaining better functional results.—Ed.]

The later treatment is instituted the less satisfactory are end results, because of excessive damage of cartilage resulting from improper drainage related to formation of pockets by adhesions.[803] Results were generally poor in some series of cases.[825, 1518] After study of 147 suppurating hips in 132 patients, Harmon and Adams [767] concluded that the course was benign in patients less than three years of age, in those with minimal or no bone involvement, and in those who had early arthrotomy with prolonged continuous extension. Positional correction of a single ankylosed hip, subsequent ankylosis of a painful hip, and certain plastic operations in juveniles were more satisfactory to Harmon and Adams [768] than arthroplastic procedures. A reconstruction operation for dislocation of hips secondary to suppurative arthritis utilized potential growth of the upper part of the femur in the very young (Harmon).[762] An arthroplasty for ankylosed knees and elbows in which the joint was reshaped into a simple ginglymus was described (Hass).[793]

Penicillin and Sulfonamides in the Treatment of Bacterial Arthritis Exclusive of Gonorrhea

The effectiveness of sulfonamides against infectious arthritis due to pyogenic streptococci and *Escherichia coli,* was confirmed in one report (Bauer, Ropes and Short [95]). But the impression of its authors that staphylococcic and meningococcic arthritis could be effectively treated by sulfonamides was not upheld by others (Frankel and Larkum; Fox and Gilbert [582]).

That penicillin is even more efficient against infectious arthritis than sulfonamides was indicated by many.[162, 451, 829, 831] Following intramuscular administration penicillin is present in adequate amounts in the synovial fluid.[63, 1182] By intra-articular injection of 25,000 units of penicillin a therapeutic level was maintained for two days thereafter.[1182] The development of arthritis in certain cases of meningococcic meningitis was not prevented, nor once established, was its course materially altered by penicillin (Rosenberg and Arling).

Postscarlatinal Rheumatism

In most cases postscarlatinal rheumatism is now generally recognized as being identical with rheumatic fever (Bradley; Watson, Rothbard and Swift [1885]).

Among 110 naval personnel with scarlet fever were 22 with pronounced electrocardiographic changes comparable to those seen in rheumatic fever: 19 had clinical manifestations of rheumatic fever. As a reaction to one or more immunizing doses of scarlet fever toxin 181 nurses developed articular pains. Among them, as compared to a control group who did not develop such reactions, there was a higher incidence of past and subsequent rheumatic fever and of rheumatic carditis (Rhoades and Afremow).

Rat Bite Fever (Haverhill Fever; Sodoku)

Much evidence suggests that a similar clinical syndrome (rat bite fever) may result from infection with either the *Spirillum minus* (Sodoku or Japanese rat

bite fever) or *Streptobacillus moniliformis* (Haverhill fever).[225, 1955, 1965] The clinical,[22, 1010, 1497, 1955] bacteriologic and laboratory features [225] of the two types of infection were differentiated.

Haverhill Fever. This disease due to *Streptobacillus moniliformis* is the more common form of rat bite fever but may occur without the bite of a rat or other animal. With special media [225] positive blood cultures for the Streptobacillus have been obtained.[22, 219, 901, 943, 1476, 1893, 1955] The agglutination test for *Streptobacillus moniliformis* is a supplemental diagnostic procedure.[103, 225, 781, 1068] The bacteriology of the Streptobacillus and its relation to the pleuropneumonia-like organism of Klieneberger were considered (Brown and Nunemaker [225]). Acute arthritis occurred in 12 of 20 collected cases [22]: in three cases it lasted 53 days, eight months and more than two years respectively. Chief visceral lesion in a fatal case of Haverhill fever was focal myocarditis; sulfadiazine had been of no value (Blake, Horstmann and Arnold).[151] But penicillin is effective. Of 86 mice infected with this Streptobacillus, all of 43 treated with penicillin, but only one of 43 not so treated, survived (Heilman and Herrell). Patients with this infection treated with penicillin have all recovered promptly.[22, 219, 809, 943, 1476, 1893]

Sodoku. This form of "rat bite fever" was transmitted by the bite of a kitten [1762] and a squirrel.[433] The *Spirillum minus* was identified by direct darkfield examination of venous blood [1488] and of material from the wound.[256] A diagnosis of Sodoku is usually made by inoculating noninfected mice and guinea pigs with patient's blood or tissue from the lymph node.[110, 700, 1336, 1794, 1955, 1965] The Weil-Felix agglutination was positive in experimental rat bite fever due to *Spirillum minus* but agglutination of "Proteus OXR" was not demonstrated in human infections.

Arthritis rarely occurs in this type of rat bite fever. Unusual "gummatoid lesions" of Sodoku within muscles and periosteum were described (Vakil; Patel). [Laboratory confirmation of the clinical diagnosis was lacking.—Ed.] Necropsy findings in an infant 11 days old with *Spirillum minus* infection and bronchopneumonia were given.[700] Penicillin is effective against the *Spirillum minus:* 25 experimentally infected mice were free of infection one day after treatment, but in the blood of 25 infected untreated mice spirilla were present during 37 days of observation (Heilman and Herrell). No case of *Spirillum minus* infection of humans treated with penicillin was reported.

Rarer Forms of Specific Infectious Arthritis

With Variola (Smallpox). Arthritis resulting from smallpox infection (Narasimhan) or vaccination (Kini and Kesavaswamy) was observed. Frank osteomyelitis and suppurative arthritis followed secondary pyogenic infection of the pustules in several cases. Juxta-articular and diaphyseal osseous lesions specifically due to the smallpox virus also were described: aseptic necrotic foci in shafts of long bones at the metaphyseal or epiphyseal ends of bones, causing arrest in growth of bone and in some cases bony ankylosis. Absorption of the epiphysis in other cases resulted in extensive deformity, but fair residual motion was preserved.

"Dysenteric Arthritis." Five cases occurring six weeks to eight months after the subsidence of bowel symptoms were described (Bonnin and Kay). The arthritis was presumably related to a "carrier" infection of the bowel with Flexner's *Bacterium dysenteriae.* Eradication of the latter infection resulted in full recovery. [Culture and examination of the synovial fluid were not done in any of

these cases. Hence the type of joint disease present remains in doubt.—Ed.] Sulfonamide was considered ineffective (Bauer, Ropes and Short).

Granuloma Inguinale and Lymphogranuloma Inguinale. Concerning these two different diseases confusion exists because of the similarity in the "ill-advised terminology" [1492] and because of certain superficial clinical resemblances. But the causes, clinical course and complications of the two conditions are different.[697, 1492]

1. Granuloma Inguinale; Granuloma Venereum. This is primarily a disease of the skin and subcutaneous tissues, usually of the inguinal region, caused by Donovan (*not* Leishman-Donovan) bodies. Despite its name it is not a venereal disease. Only occasionally does secondary nonspecific involvement of adjacent lymphatics occur. Systemic reactions and articular manifestations are rare or at least rarely mentioned. However, granuloma inguinale may be a systemic as well as a local disease, and Lyford, Scott and Johnson [1137, 1564] reported a case of polyarthritis (ulceration of many joints, widespread destruction of bones) in which Donovan bodies were found in articular tissues and bone, also a second case with involvement of two vertebrae and a hip joint communicating with sinus tracts presenting in the inguinal regions. In these cases the onset of migratory polyarticular pain, swelling and effusions was insidious. At one stage disease in the joints resembled "typical rheumatoid arthritis," but months later articular swellings ruptured through skin leaving a granulating ulceration. An elbow was explored; synovia was thickened and friable, but cartilages were "clean and smooth." Articular tissue contained Donovan bodies in macrophages, and large numbers of plasma cells in exudate.

Orthodox treatment was discussed (Greenblatt [697]; Root [1492]).

2. Lymphogranuloma Inguinale; Lymphogranuloma Venereum; Lymphopathia Venereum. This venereal disease, due to a filtrable virus, is primarily one of local (generally inguinal) lymphatics and surrounding connective tissue with secondary involvement of overlying skin and often constitutional and systemic manifestations including arthritis and anorectal strictures. A specific skin reaction to an antigen made from material aspirated from bubo (Frei test) occurs. The primary lesion is usually genital; the second stage comprises acute lymphadenitis (bubo); the tertiary (chronic) stage involves chronic granuloma, lymphatic progression and secondary infection to distant sites including joints ("exudative arthritis") and rectum (strictures) (Greenblatt; Root).

Among the constitutional evidences arthritis was prominently mentioned.[827] A case with chronic arthritis involving "nearly all joints, without causing much deformity" was described.[1338] [No further details.—Ed.] Hickam [840] described articular manifestations under three categories: 1. Migratory arthralgia, usually fleeting, without objective joint changes is common in early weeks of infection. 2. Acute polyarthritis, painful swelling, redness and increased heat may accompany early or later stages of the disease. Ankles, hips, elbows and wrists are most often affected. The arthritis disappears rapidly without residues. Sometimes acute migratory arthritis may be evoked by a Frei test. 3. Chronic recurrent polyarthritis with effusions, in the later stages of the disease without deformity or functional impairment may occur. In this stage also effusions may follow the Frei test.

General articles appeared without special reference to joints,[135, 697, 698, 950, 1152, 1194, 1987] also studies on the diagnostic value of laboratory tests.[361, 685, 917, 1486] Treatment of the various stages and of nonarticular complications was discussed.[206, 391, 697,

[698, 827, 920, 1024, 1338, 1573] Sulfonamides (sulfathiazole or sulfadiazine) were the drugs of choice. Sulfonamides combined with Frei antigen were considered of special value by some (Costello and Chen). Penicillin was ineffective (Mann).

Miscellaneous. Hemophilus influenzae was recovered from the knee of an infant 15 months old. Suppurative arthritis developed on the second day of an acute respiratory infection (Bercovitz). Suppurative periarthritis of the shoulder in an infant due to *Bacillus suipestifer* was described with a review of the literature (Guthrie). "Chronic arthritis" related to *Pseudomonas pyocyanea* infection of intestines was reported with "cure following autovaccine therapy" (Fiset). [Data presented did not prove an etiologic relationship.—Ed.]

Mycotic Diseases of Joints

Coccidioidomycosis; Coccidioidal Arthritis. Coccidioidomycosis, still rare, is of increasing interest as a cause of disease of bones and joints. The disease was originally confined to the San Joaquin Valley of California and most cases have originated in that state, 660 cases having been reported there up to 1941. But the disease has appeared in at least 16 other states, notably Texas and Arizona, and a new case was reported from Louisiana.[1551] Infection occurs by inhalation of dust carrying endospores of *Coccidioides immitis,* the initial lesion being pulmonary. This may produce a symptomless infection, never recognized (as in most of the residents), or after an incubation period of eight to 21 days acute pneumonitis may develop which usually heals with fibrosis, occasionally with cavitation. Its relationship to coccidioidomycosis is generally not recognized and it is diagnosed "influenza" or "pneumonia." [1407, 1947] During this pulmonary infection a relatively permanent skin sensitivity to the organism develops as indicated by positive coccidioidin test. The mortality rate of the acute pulmonary infection is less than 1 per cent. Of 736 soldiers stationed at Camp Roberts on the Western slope of the Coast Range Mountains of California, a region not previously known to be infected, 14 (2 per cent) had coccidioidomycosis (four symptomless; 10 with mild respiratory infection; Shelton [1595]).

About 2 to 5 per cent of those who have acute respiratory symptoms demonstrate clinically an "allergic reaction" two to 20 days later, characterized by fever, "arthritis," articular and muscular pains, often conjunctivitis and erythema nodosum with or without erythema multiforme. This reaction has been termed "desert rheumatism," "desert fever," "valley fever," "San Joaquin fever." Joints are tender, painful and slightly swollen but no effusion occurs and after about a month symptoms disappear without articular residues.[671, 672, 1501, 1925]

In the vast majority of cases nothing further develops but in about 0.05 to 0.3 per cent coccidioidomycosis becomes systemic,[672, 1190, 1407, 1501] a progressive "secondary," disseminated infection known as coccidioidal granuloma, chronic granulomatous coccidioidomycosis, "San Joaquin Valley disease," "California disease." [1637] The rate of dissemination was "unbelievably high" (12 per cent) among the 49 cases of Willett and Weiss. Depending on the site or sites to which the fungus spreads granulomatous lesions occur in soft tissues, bones or parenchymatous organs commonly affecting meninges, bones, joints, muscles, skin and so forth.[125, 401, 991, 1501, 1925] The mortality rate of "the dread granuloma" is 50 to 60 per cent; annually 46 such cases are reported in California (Shelton).[1595] In recent cases joints,[280, 1154, 1190, 1501, 1641] multiple osseous sites including vertebrae, skin, liver and kidneys,[1357, 1551] have been

involved. In one case both ankles were affected; in roentgenograms the lesions resembled somewhat tuberculous arthritis but biopsy revealed the fungus.[1501] Granulomatous involvement of femur with secondary abscess of hip joint developed in one case (Martin).[1160] In another case articular pains lasted several months after the acute pulmonary phase (Bush).[267] In 79 of 256 collected cases of the chronic granulomatous phase, the joints were affected, ankles, knees and feet most frequently (Rosenberg, Dockerty and Meyerding[1501]). Joint involvement may be purely synovial, or synovial with subarticular destruction indistinguishable from tuberculosis (Benninghoven and Miller). The locations and nature of osseous lesions in more than 100 collected cases were discussed.[125]

Treatment for the acute pulmonary disease with arthritis and erythema nodosum consisted of rest, salicylates[1637] or convalescent serum.[671] There is no known remedy for the chronic granulomatous phase[1637, 1641]; penicillin and roentgen therapy were ineffective[1501] against the coccidioidomyosis but penicillin may control secondary infections.[460]

Actinomycosis. A patient sprained his ankle; an actinomycotic abscess of the ankle developed and failed to heal after incision. Later the disease spread to heart and other organs. Diagnosis was first made at necropsy (Gose).

Actinomyces may enter the body via skin, lungs or intestines. From any primary focus they may reach vertebrae usually by direct invasion, occasionally by blood stream. In vertebrae a paravertebral phlegmon develops which may produce an abdominal lesion resembling tuberculous psoas abscess. Vertebral actinomycosis is rare; only about 50 cases have been reported, most of which were regarded as Pott's disease before necropsy. But roentgen findings are "characteristic if not definitely diagnostic": areas of destruction in all parts of the vertebra with surrounding sclerosis. Despite extensive destruction, vertebral collapse is rare; even then intervertebral disks are spared. Three cases were reported (Lubert).

The heart may be reached by metastasis or by direct extension, commonly from lung. Actinomycosis of heart may simulate rheumatic heart disease (Cornell and Shookhoff; Gose; Lidbeck).

Histoplasmosis. This chiefly affects the reticulo-endothelial system. Caused by the fungus, *Histoplasma capsulatum,* lesions occur notably in liver, spleen, lymph nodes, bone marrow and lungs. Fever, anemia, leukopenia, emaciation, enlargement of liver and spleen result. The fungi are found in cytoplasm of circulating monocytes, in tissue phagocytes and elsewhere. Presumably the first case in which joints were involved was noted by Key and Large.[998] The case resembled tuberculous arthritis but tuberculin test and guinea pig inoculation were negative. The leg was amputated; 10 days later death resulted from pneumonia and cardiac failure. The diagnosis was not suspected until examination of synovial tissue revealed the Histoplasma.

Rheumatic Fever

Incidence. Determination of the incidence of rheumatic fever is handicapped because the disease is generally not reportable. However, useful and reasonably accurate estimations were reported.

Keith[965] estimated that rheumatic heart disease affects 0.10 to 2.08 per cent of British, 0.9 to 1.36 per cent of American and 0.36 to 3.92 per cent of Canadian, school children. In New York City from 1936 through 1938, 681 deaths from rheumatic

fever, or rheumatic heart disease, were recorded in children five to 14 years of age.[1158] This number exceeded deaths from accidents for that age group and was two and one-third times greater than deaths from infantile paralysis, pulmonary tuberculosis, scarlet fever, measles, whooping cough and diphtheria combined. Martin[1158] estimated that 1,000,000 people in the United States had rheumatic carditis which caused 40,000 deaths yearly at the average age of 30 years. The incidence of rheumatic heart disease in school children ranged between 0.7 and 1.0 per cent. Rheumatic fever with rheumatic heart disease was the leading fatal disease from the ages of five through 19 years.[39, 1226, 1229] For each 100,000 men examined for selective service 340 were rejected with the main diagnosis of rheumatic heart disease (Rowntree). The actual incidence was much higher as many men were rejected for obvious defects who also had rheumatic heart disease; also, in many cases it was not detected at the initial examination. Fifty per cent of all men rejected for cardiovascular diseases had rheumatic heart disease. Shaffer found rheumatic heart disease in 1 per cent of 25,000 selectees. Levy, Stroud and White reported that of the men rejected because of heart disease, rheumatic heart disease was responsible for 51 per cent in Boston, 70 per cent in Chicago, 64 per cent in New York, 70 per cent in Philadelphia and 40 per cent in San Francisco. The Children's Bureau estimated that in this country 500,000 children are handicapped by rheumatic fever and rheumatic heart disease (Lenroot).

In England deaths from rheumatic fever declined from 23 per 1,000,000 (all ages) in 1939 to 12.1 in 1942 (Glover). In the United States the deaths from rheumatic fever and rheumatic heart disease in persons aged five to 24 years fell from 32.3 per 100,000 in 1917 and 1918 to 9.7 in 1943 (Metropolitan Life Insurance Company[1227, 1228]). Each five-year period since 1922 has shown a lowered mortality rate and decrease in the percentage and severity of cardiac damage.[11]

Predisposing Factors Governing Incidence. 1. Geography and Climate. Reports agreed that rheumatic fever is more common and severe in temperate than in warmer climates. The influence of geography and climate was investigated by three standard routines: (1) comparison of the incidence of rheumatic fever among comparable groups; (2) comparison of hospital admission rates, and (3) analysis of necropsy data. The opportunity to study the incidence of rheumatic fever in troops in various geographic areas during the past war added greatly to our knowledge of geographic incidence. Maps prepared from the Surgeon General's report[1454] showing the incidence of disease at different posts illustrated the marked difference in the frequency of rheumatic fever in the North as compared to the South. The Army Air Forces surveyed 40 posts scattered throughout the United States and found a strikingly high incidence of the disease in the Rocky Mountain area, Great Lakes area, and Midwest, with a low incidence along the Mexican border and Gulf of Mexico (Holbrook and van Ravenswaay[855, 856]).

Climatic factors are exceedingly complex and comprise many other factors than latitude, as was illustrated by a study of the incidence of rheumatic fever in school children in three California cities with different climatic factors. In Eureka, a north California sea coast town with a fairly high rainfall but equitable temperature, the incidence of rheumatic heart disease among school children was 2 per cent; in Susanville, at an altitude of 4,268 feet with moderate rainfall, it was 1.1 per cent; in Redlands, with an altitude of 1,350 feet and relatively dry, it was only 0.38 per cent (Sampson, Hahman, Halverson and Shearer). Paul[1348] found 10 times as much rheumatic heart disease among Indian school children near the Canadian border as was present among Indian school children living near the Mexican border.

Although rheumatic fever and rheumatic heart disease are less frequent in the southern states and in the tropics, the incidence there is such that attention should be paid to the problem.[285, 293, 734, 770, 1055, 1187, 1225, 1229, 1471, 1602, 1819, 1880, 1914]

Data on comparison of hospital admissions were summarized: The percentages

of children admitted with rheumatic fever or rheumatic heart disease were as follows: Philadelphia 5.8; Portland, Oregon 3.5; Cincinnati 2.7 [1896]; Dallas 0.8 [544]; Los Angeles 0.69.[441] The percentages of total admissions to general hospitals for rheumatic fever or rheumatic heart disease were as follows: Galveston, Texas, 1930–1939, 0.2 [452]; Vizagapatan, India, six-year period, 3.5.[1052, 1053] In Galveston rheumatic heart disease during 1930–1939 constituted only 2.1 per cent of total cardiac admissions (Decherd and Herrmann). These low findings contrast with those of Chavez [311] in Mexico who reported that in charity cases rheumatic heart disease constituted 62 per cent and in private cases 41 per cent of the total cardiac cases. "These are tremendous differences for which some explanation must be sought."

Comparable necropsy studies, reported from various geographic areas, are summarized giving the incidence of rheumatic heart disease: in Boston 5.5 per cent (456 of 8,300 necropsies [634]); in Atlanta 3.5 per cent (61 of 1,754 necropsies [820]); in Galveston 0.9 per cent (22 of 2,463 necropsies [452]); in New Orleans 0.63 per cent (102 of 16,121 necropsies [231]).

Four times as much mitral stenosis was found in Atlanta as in New Orleans although the economic level of the patients in the two hospitals studied was comparable (Claiborne and Wolff [320]).

The incidence of rheumatic carditis among Denver high school girls was 16.3 per 1,000 (Wedum, Wedum and Beaghler [1899]). Denver was said to have the second highest death rate from rheumatic heart disease among the 25 largest American cities.

2. Season. In the temperate zone the greater prevalence of rheumatic fever in winter and spring was reaffirmed.[1226, 1227, 1348, 1349] No seasonal variations occurred in India.[1052]

3. Social and Hygienic Factors. The greater frequency of rheumatic fever among low income groups was again noted.[878, 1159, 1264, 1348, 1349, 1360, 1503, 1906] The importance of crowding was stressed.[1229, 1273, 1898, 1920]

4. Family, Heredity and Constitution. The familial tendency of rheumatic fever was again supported by Wilson and her colleagues [1940, 1942]; its distribution followed the general laws of recessive mendelian inheritance. Others considered the familial factor important.[276, 277, 1174, 1229, 1347, 1503] But some observers from various parts of the country found no significant familial incidence.[721, 1052, 1906] The familial incidence was variously reported as being 5.7 (compared to 3.6 among controls),[1530] 7.6,[379] 8.9 [441] and 12 per cent.[907]

5. Sex. The incidence is essentially the same in both sexes, if chorea is excluded.[351, 1055, 1348] The death rate among males is a fifth greater than among females (Metropolitan Life Insurance Company [1228, 1229]).

6. Age. The peak incidence and average age of onset was at eight years [351, 512, 721, 886, 925, 1158]; currently the oldest patient with an initial attack of acute rheumatic fever was 61 years of age (Rakov and Taylor [1428]) and the youngest was a newborn infant 10 days old (Denenholz and Rambar).

7. Race. As to racial differences opinions varied. The incidence of rheumatic fever and carditis was about the same among Negroes and whites in New Orleans,[231] also in Louisville, Kentucky,[1906] greater among the Negroes in Cincinnati,[1897] and less among the Negroes than whites in Philadelphia.[806]

General Symptomatology and Relative Incidence of Various Manifestations of Rheumatic Fever

Of 1,487 cases of rheumatic fever in Chicago Gibson [650] noted polyarthritis in 983, chorea in 581, rheumatic nodules in 156, carditis in 864. Other rheumatic manifestations affected 74 per cent of the polyarthritic patients, 56 per cent of the choreic patients, all of those with rheumatic nodules and 84 per cent of those with carditis.

Of 583 children with rheumatic heart disease the initial manifestation was acute carditis in 8 per cent, polyarthritis in 60 per cent, chorea in 20 per cent, myalgia and joint pains in 10 per cent, insidious carditis in 9 per cent (Ash [41]). Pain in a joint of the lower extremity was the initial symptom in most of Kimbro's 100 cases. Sometimes this was so mild that the patients had been referred for flatfeet. In a study of 1,754 necropsies of rheumatic heart disease a past history of articular involvement was noted in only 29 per cent (Claiborne and Wolff). But Shapiro [1590] obtained a history of arthritis in all but 2 per cent of his cases, and Martin [1158] failed to obtain a history of chorea or arthritis in only 14.7 per cent. The importance of rheumatic nodules was emphasized.[68, 397, 1739] All of the 167 patients with rheumatic fever with nodules studied by Hayes and Gibson presented some other manifestation of rheumatic fever and 163 had definite signs of heart disease.

Pathology of Rheumatic Fever: General Considerations and Clinicopathologic Data

Cardiovascular System. The incidence of rheumatic stigmata in hearts presumably normal, nonrheumatic and obviously free of gross valvular lesions was found on microscopic examination by Hall and Anderson to be surprisingly high. In 90 per cent of 112 such grossly normal hearts from persons without clinical evidence of rheumatic infection or valvulitis, rheumatic myocardial lesions were found in close proximity to mitral valves. All the well-known rheumatic stigmata were "abundantly present" including Aschoff bodies in 30 per cent.

[These figures are indeed surprising unless we are to believe that 30 to 90 per cent of all hearts show (at least microscopic) evidence of rheumatic carditis. Otherwise these lesions will have to be regarded as nonspecific tissue responses to various insults, not necessarily to the "rheumatic virus."—Ed.]

The relationship between Aschoff bodies and rheumatic activity was noted by Console who studied 98 cases in which endocarditis or pericarditis was found at necropsy and in which there was a history of rheumatic fever. Aschoff bodies were found in all in which death occurred in the first decade of life, in 64 per cent in the second decade of life, and in 11 per cent of those in later life. When Aschoff bodies were found, the last attack of polyarthritis preceded death by five months or less. In three cases there was no history of rheumatic fever despite the presence of Aschoff bodies.

Stokes-Adams attacks in a child with insidious rheumatic pericardial effusion [1716] and intermittent bundle-branch block in a case of acute rheumatic fever were reported.[787] In cases of chronic rheumatic heart disease auricular fibrillation may be due to substitution of the auricular smooth muscle for striated cardiac muscle.[888]

Of 2,476 persons with rheumatic valvular disease rejected by draft boards in five cities and studied by special boards of review, 750 had mitral regurgitation alone, 750 had mitral stenosis alone, 208 had aortic regurgitation alone, 72 had aortic stenosis alone, 628 had combined mitral and aortic disease; 68 had unspecified lesions (Levy, Stroud and White [1090]).

Pericarditis is an ominous sign according to Ash [42]; 75 per cent of 553 children with rheumatic pericarditis who were observed for 9.6 years died.

The presence of occasional upper respiratory infections, articular symptoms and high antistreptolysin titers in 10 persons less than 30 years of age who died of myocardial infarctions suggested to Weinstein that some infarctions are of rheumatic origin. The possible rheumatic origin of certain coronary lesions and of angina pectoris in young persons was noted also (Ernstene and Schneider; King [1004]).

Joints. No new data appeared. [It is unfortunate that so little is known about the pathology of joints in rheumatic fever. Surely enough patients die either during acute rheumatic polyarthritis or sufficiently soon thereafter that much data could be learned by examination of articular tissues as well as heart at necropsy. Why are pathologists so loathe to invade joints when they invade without compunction the more "sacred" heart and brain?—Ed.]

Lungs and Pleura. There is "no specific rheumatic pneumonia" [530] according to some but others disagreed.[1202] The "Masson body" is not specific [824] but was believed to be due to capillary damage with altered permeability. The following were noted: hemoptysis in 10 per cent of cases of rheumatic heart disease, and pulmonary arteriosclerosis.[1958]

Skin and Mucosa. Erythema marginatum [397] and erythema multiforme each occurred in 1.9 per cent of rheumatic patients; the presence of erythema multiforme was considered a poor prognostic sign.[1739]

Nervous System. The relation of the nervous system to, and the late cerebral sequelae of, rheumatic fever were again discussed (Bruetsch [228]).

Rheumatic carditis occurs with unusual frequency in the mentally ill but its incidence differs somewhat with the type of mental illness: 9 per cent in cases of schizophrenia; only 1.7 in cases of dementia paralytica. Unsuspected rheumatic carditis, "rheumatic encephalitis," cerebral embolism, and cerebral obliterative endarteritis often is revealed at necropsy on psychotics.[229, 486] Meningoencephalitis, with an inflammation "compatible with that of rheumatic fever" was noted in a case of fatal, proved rheumatic fever.[842]

In 29 cases of rheumatic carditis (in 59 per cent of which Sydenham's chorea had occurred) convulsive disorders presumably rheumatic developed.[577] The term "rheumatic epilepsy" was applied by Bruetsch [227] to convulsive seizures following rheumatic fever or chorea, and for epilepsy associated with chronic rheumatic valvulitis.

Chorea and its relationship to rheumatic fever will be discussed separately.

Kidneys. Rheumatic patients with renal insufficiency and necropsy findings of focal glomerular nephritis and arteritis, and diffuse obliterative renal vascular disease were noted (Hutton and Brown).

Eyes. "There is no ocular pathologic change pathognomonic of rheumatic fever" (Rudolph [1517]).

Testes. Trasoff and Goodman [1807] reported a case of "rheumatic orchitis" associated with rheumatic pericarditis. [There is no proof of the rheumatic origin of the orchitis.—Ed.]

Laboratory Data in Rheumatic Fever

Electrocardiogram. Abnormalities were reported in from 50 to 77 per cent of cases of rheumatic fever [987, 1327, 1910] and in 39 per cent of cases of Sydenham's chorea.[807] Carotid sinus pressure produced increased impairment of the atrioventricular conduction time in 12 of 16 patients with active rheumatic carditis. Administration of prostigmine augmented the response.[712] Wendkos suggested the intravenous use of ergotamine tartrate (gynergen) to increase the diagnostic precision of the electrocardiograph in rheumatic fever. Atropine is of no help in distinguishing P–R intervals prolonged by vagotonia from those prolonged by rheumatic fever, because atropine reduces the P–R time equally in both.[1485]

Sedimentation Rate of Erythrocytes. Formol Gel Test and Weltman Reaction. The sedimentation rate is the most sensitive test of rheumatic activity.[322, 650, 1013, 1244, 1879] It is seldom increased in chorea unless other rheumatic manifestations are also present.[120, 322, 1590] Nine of Harris'[778] 400 patients with rheumatic fever continued to have high sedimentation rates long after all other evidences of activity of the disease had subsided. An abnormal Weltman reaction, especially a shortened coagulation band, was found by Scherlis and Levy to be more frequently associated with rheumatic activity than was an elevated sedimentation rate. Otherwise the tests were statistically about equal. Formol gel tests were less sensitive and of less value in determining rheumatic activity than sedimentation rates.[270, 1013]

Blood Counts. The nonfilamented neutrophile count was of less value than the erythrocyte sedimentation rate.[1879]

Capillary Resistance. This was found generally to be low in 150 rheumatic children (Brown and Wasson). It varied with changes in temperature and barometric pressure.

Blood Salicylate Level. A method for the determination of salicylic acid in plasma was described.[216, 330]

Serum Proteins. Changes in serum protein in scarlet fever and rheumatic fever were qualitatively similar.[475] Albumin-globulin ratios were sometimes inversed.[1527]

Blood Sugar. Following tolerance tests, sugar curves suggesting hyperinsulinism were found in 11 cases of rheumatic fever (Abrahamson[5]).

Relationship of Rheumatic Fever to Other Diseases

Rheumatoid Arthritis. The relationship of rheumatic fever to rheumatoid arthritis has been the subject of conflicting reports. At necropsy evidence of rheumatic heart disease was found in 16 (53 per cent) of 30 rheumatoid patients, according to Baggenstoss, Rosenberg and Hench[53, 54, 1500] who concluded: "This evidence suggests ever more strongly that rheumatoid arthritis and rheumatic fever are in some manner closely related." A similar conclusion was made by Young and Schwedel who found "rheumatic heart disease" in 25 (66 per cent) of 38 necropsies in cases of rheumatoid arthritis. But Bennett[122] arrived at quite a different conclusion from his study of necropsies on 101 patients with rheumatic fever and 48 patients with rheumatoid arthritis: "It is apparent that the usual anatomical changes observed in rheumatoid arthritis differ so markedly from those of rheumatic fever that one must infer that the pathogenesis of the observed lesions is different."

[This topic is discussed further under "Pathologic Characteristics of Rheumatoid Arthritis" and "Relationship of Rheumatoid Arthritis to Rheumatic Fever."—Ed.]

Subacute Bacterial Endocarditis. The recurring arthralgia and arthritis seen in some patients with endocarditis caused by *Streptococcus viridans* were considered as being due to complicating acute rheumatic fever or the "general toxemia caused by bacterial endocarditis." The latter was held more likely in view of the unusual clinical features and the failure to respond to the usual forms of therapy for rheumatic fever (Christian[317]). [Many patients dying of subacute bacterial endocarditis are found to have coexisting rheumatic fever at necropsy.—Ed.]

In 25 per cent of 452 fatal cases of rheumatic heart disease postmortem evidence of bacterial endocarditis was noted (Gelfman), and rheumatic carditis was present in 90 per cent of 174 consecutive adult patients with subacute bacterial endocarditis (Christian[316]). The rheumatic heart lesion was called the "determinative background for bacterial endocarditis."

Erythema nodosum. No evidence supported the theory that erythema nodosum is a manifestation of acute rheumatism. Perry [1882] found only 10 cases of erythema nodosum in more than 1,000 patients with acute rheumatism.

Miscellaneous Diseases. The relationship of rheumatic fever to glomerulonephritis,[1572] scarlet fever,[203, 1885] scarlet fever immunization,[1455] rubella [1281] and fibrositis [879] was discussed.

Differential Diagnosis in Rheumatic Fever

Data to be considered in the diagnosis of rheumatic fever were tabulated by Jones [924] who listed five major manifestations (carditis, arthralgia, chorea, subcutaneous nodules and febrile rheumatic recurrences) and seven minor manifestations (fever, abdominal pain, precordial pain, rashes, epistaxis, pulmonary findings and laboratory data). Any single major manifestation with at least two minor manifestations would place the diagnosis on reasonably safe grounds. Similar criteria were emphasized by Barnes and by Griffith.

Hansen [750, 751] compared the admission diagnosis with the final diagnosis in 271 cases of supposed rheumatic fever among children. One-third of the initial diagnoses were incorrect. The most probable causes of error in the order of frequency were: abdominal pain with possible appendicitis, acute anterior poliomyelitis, acute osteomyelitis, skin eruptions and nephritis.

The abdominal pains of rheumatic fever were discussed.[35, 129, 1450] There are no abdominal signs which warrant clear-cut differentiation between suppurative appendicitis and rheumatic "pseudo-appendicitis." But estimations of the sedimentation rate are helpful as the rate tends to be normal in suppurative appendicitis but sharply increased in rheumatic pseudoappendicitis (Langmann). Differentiation between nonrheumatic "growing pains" and rheumatic joint pains was again discussed.[41, 282, 579, 650, 1590] Acute rheumatoid arthritis, Still's disease, disseminated lupus erythematosis, brucellosis, coccidioidomycosis and subacute bacterial endocarditis occasionally demand the utmost in diagnostic acumen in making a differential diagnosis.[76, 750, 751, 924, 1454] A case of actinomycosis of the heart simulating rheumatic fever was described.[389]

Course, Prognosis and End Results of Rheumatic Fever

The disease was severe in a third, moderately severe in a half, and mild in a fifth of 54 Boston cases (Bland). The average duration of active infection was eight months, but three patients required rest in bed for two to two and one-half years. Of 553 children with rheumatic fever followed by Ash [41] for an average of nine years 71 per cent showed signs of heart disease at one time but because of regression of such signs a diagnosis of organic valvulitis was eventually made in only 64 per cent. Twenty-six per cent had died. First attacks of rheumatic fever are more likely to cause carditis in children than in adults.[40, 957, 966, 1463, 1590] Deliee, Dodge and McEwen found residual cardiac damage in 7 per cent of 67 adults and in 28 per cent of 78 children. The incidence of heart disease varies also with the clinical type. Children whose disease began with acute carditis had the highest initial mortality: 65 per cent were dead in 10 years.[41, 42]

Records of 3,129 patients with fatal rheumatic heart disease were analyzed by Cohn and Lingg. The average duration of disease was about 13 years. Fifty per cent died within nine years after onset, 25 per cent lived more than 17 years and 10 per cent for 30 years or more. Whereas Cohn and Lingg analyzed only fatal cases, Martin [1158]

studied a group of 1,438 children with rheumatic heart disease; 30 per cent were dead after 20 years, 43 per cent of the deaths occurred within five years of the initial rheumatic attack; more than two-thirds succumbed before the age of 16 years.

In a follow-up of 1,000 patients with rheumatic fever Jones and Bland found that at the end of the 10 years 31.3 per cent had no detectable heart disease; 47 per cent had some degree of rheumatic heart disease; 20.3 per cent had died, mostly as the result of recurrent rheumatic fever; follow-up data in 1.4 per cent were inadequate. Of the 1,000 patients, 64.8 per cent were able to lead relatively normal lives 10 years after the onset of rheumatic fever. [An interesting and reassuring study.—Ed.]

Studying 499 rheumatic patients during 5,677 "person-years" Wilson and Lubschez found only two factors which influenced the risk of future recurrences: the age of the child and the interval of time elapsing since the last attack. It was calculated that the risk of recurrence during the year immediately following a major episode is 38.7 per cent compared to 11.2 per cent in the year after one year of freedom. Similar figures were presented by Ehlertsen, but Cohn and Lingg in their analysis of more than 3,000 patients concluded that recurrences are most prevalent before puberty regardless of the interval of freedom.

Auricular fibrillation in cases of rheumatic heart disease which had lasted 12, 13 and 15 years was reported (Kosamann and Connor). Other interesting clinical and statistical reports cannot be reviewed here.[40, 42, 153, 224, 397, 650, 656, 934, 966, 1176, 1769, 1777, 1921]

The important but well-known signs of activity and quiescence of rheumatic infection were reviewed.[87, 153, 282, 966, 1777, 1881, 1974]

Etiology and Pathogenesis of Rheumatic Fever

Factor of Infection. 1. Streptococcic Infection. Further evidence favored hemolytic streptococci as a direct, or indirect, cause of rheumatic fever.[547, 693, 694, 878, 1174, 1176, 1455, 1686, 1919] The great tendency of upper respiratory infections to induce rheumatic attacks[153, 691, 1050, 1768] and the close relationship of epidemics of hemolytic streptococcic infections and rheumatic fever in the armed forces were noted.[331, 691, 855, 912, 1969]

The carrier rate for Group A hemolytic streptococci in well troops was shown by Van Ravenswaay to parallel rather closely the incidence of rheumatic fever. Of 38 clear-cut and nine questionable rheumatic occurrences observed by Kuttner,[1048] all 47 followed streptococcic upper respiratory infections. The relationship of postscarlatinal arthritis and carditis to rheumatic fever was noted: in 19 of 110 cases of scarlet fever abnormal electrocardiograms were noted during convalescence (Watson, Rothbard and Swift[1885]). Only eight of the 19 patients had definite clinical attacks of rheumatic fever but the authors believed that, following their streptococcic infection, all suffered from the same fundamental tissue injury characteristic of rheumatic fever. Rheumatic fever may long remain active in a subclinical form; respiratory infections are important only in such cases; in really inactive cases respiratory infections were not followed by recurrences (Juster[937]). Thomson and Glazebrook did not find a definite parallelism between the occurrence of rheumatic fever and epidemics of tonsillitis in a semiclosed community. Green[693] recovered hemolytic streptococci from the valves with microscopic lesions of rheumatic fever in eight of nine cases.

Serologic reactions in cases of rheumatic fever continued to suggest a relationship

to hemolytic streptococci. Precipitin tests such as antifibrinolysin and antistreptolysin reactions tended to be the same in cases of rheumatic fever as in cases of proved hemolytic streptococcic infection.[172, 545, 692, 1101, 1266] Autoantibodies to human heart were present in the blood of 75 per cent of a group of patients with acute rheumatic fever (Cavelti).

Experimental myocardial lesions induced by *Streptococcus viridans* were not those of rheumatic fever.[709]

2. Other Infections. Copeman [379] described cases in which the infection preceding rheumatic fever was not streptococcic. Dysentery, sand fly fever and malaria at times seemed to precipitate rheumatic fever. An outbreak of influenza did not precipitate rheumatic recurrences in children.[1050, 1451] No relationship was found between acute rheumatism and epidemics of rubella, measles, chickenpox, common cold and diphtheria (Green [691]).

3. Virus Theory. The question continues to be raised whether an unidentified virus may not be the direct cause of rheumatic fever, acting in association with hemolytic streptococcic infections.[1050, 1077] Green [693] considered the evidence not positive.

4. Experimental Transmission of Rheumatic Fever. In what was believed to be the only study of its type on record Copeman [380] reported the probable transference of rheumatic fever from a patient with the disease to three of five volunteers by injecting intravenously 5 c.c. of the patient's blood into each volunteer. The blood was transferred on the fourth day of the patient's illness to five volunteers. Mild attacks of "rheumatic fever" developed in two of them after 24 hours, and pain in the shoulder muscles without pyrexia three days later in another. Blood from the two patients contracting mild rheumatic fever was pooled on the third day and again passed on to four volunteers. One of the four had an attack of febrile fibrositis on the second day. Blood from the more severely affected of the first two patients was again transferred on the seventh day of illness to four more volunteers. In one of these painful generalized fibrositis developed which six weeks later seemed likely to become chronic. Copeman [380] stated that these studies were not sufficiently controlled but that an infective agent appeared to be present in the blood of the original patient which was capable of transference to others.

[If this work can be repeated and confirmed, it will go a long way to support the virus theory.—Ed.]

Factor of Allergy and Anaphylaxis. To cutaneous injections of purified M proteins of 40 types of hemolytic streptococci 65 per cent of normal children and 83 per cent of rheumatic children gave a positive reaction (Taran, Jablon and Weyr [1770, 1771]). Struck by the relationship of periarteritis nodosa to sensitivity states, Rich and Gregory [1458, 1461, 1462] produced in rabbits, with the antigen horse serum, lesions considered identical with those of that disease. By the same means Rich [1458] produced in 19 of 51 rabbits changes in the heart which he regarded as typical of rheumatic fever: focal alterations in collagen; nonspecific inflammatory lesions in valves, endocardium, myocardium and pericardium; valvular nodular projections of swollen and degenerating collagen with damaged overlying endothelium; small foci of myocardial necrosis and myocardial lesions with the basic characteristics of Aschoff bodies. Such changes did not occur spontaneously in hundreds of other rabbits. Rich [1458] concluded that rheumatic fever is an allergic disease with a native individual difference

in reactivity which determines not only whether a hypersensitive reaction occurs in a given sensitized individual on contact with the antigen but also in what tissue the hypersensitive reaction occurs. Robinson[1481, 1482, 1483] was unable to confirm Rich's [1458] work, finding that horse serum alone did not produce a carditis like that reported by Rich.[1458] He was able to produce many lesions typical of streptococcic disease of human beings and some cardiac lesions resembling those found in human rheumatic fever by injecting sterile erythrogenic filtrate of NY–5 hemolytic streptococci into young albino rabbits. Clawson failed to confirm the work of either Rich or Robinson and found no evidence favoring the theory that streptococcic toxin acts directly or by an allergic reaction on valves. Neither was he able to produce rheumatic heart lesions from hypersensitiveness or serum sickness alone. But rats infected intracardially with *Streptococcus viridans* or hemolytic streptococci developed acute rheumatic-like endocarditis or bacterial endocarditis or both. Clawson concluded that acute rheumatic endocarditis and bacterial endocarditis occur only as a response to a direct valvular infection with bacterial cells. Other experimental work was reported.[597, 1077, 1086, 1087] Loewenstein [1118, 1119] cultured tubercle bacilli from the blood in 69 per cent of 412 cases of rheumatic fever and concluded that rheumatic fever is due to hypersensitivity to tubercle bacillus. [See the discussion on "Tuberculous Rheumatism."—Ed.]

Factor of Vitamin Deficiency. The diet of 50 patients with rheumatic fever was deficient in vitamins A and D, calcium and phosphorus.[1358] Irrespective of its previous concentration, that of vitamin A in plasma falls with the onset of rheumatic fever but the carotene content is not altered.[1587]

Patients with frank avitaminosis B in India rarely develop rheumatic fever (Kutumbiah).

The subnormal plasma content of vitamin C in rheumatic fever and the possible influence of vitamin P was discussed (Rinehart).

Hormonal Factors. A type of hormonal imbalance is a predisposing or causative factor in rheumatic fever, according to Tormey, Woods and Gallagher.[1803] This imbalance, present in certain persons at birth, "is created by disequilibria among the derivatives of the polycyclic hydrocarbon cyclopentanoperhydro-phenanthrene."

Physical Factors. Rheumatic fever may begin within a few days of trauma; the traumatized joint may be the first affected (Glazebrook and Thomson [657]). Weight-bearing joints are often first affected (Couper; Kimbro). Physical factors (exposure, cold, wet, excessive fatigue) are important predisposing factors; cases in which physical factors of extreme degree alone appear to be responsible were reported (Copeman [379]).

Conclusions on Etiology. There was considerable agreement that hemolytic streptococcic infections are related to rheumatic fever, but the mechanism of action of hemolytic streptococci remains unknown (Paul [1347]).

[From data available it appears that rheumatic fever usually occurs in a susceptible person following a hemolytic streptococcic infection in a climate having the necessary meteorologic factors. The individual's environment with regard to housing, working conditions, financial status, warmth, exposure, fatigue and so forth is also an important factor in increasing or decreasing his liability to rheumatic fever. But the exact cause of the disease remains unknown.—Ed.]

Treatment of Rheumatic Fever

Rest. For the acute phase of rheumatic fever complete rest is "the one indispensable measure"; it should be continued until all evidences of activity of the disease have disappeared.[41, 153, 252, 691, 847, 1055, 1511, 1769]

By superimposing serial roentgenograms and noting variations in cardiac size Taussig and Goldenberg were able to prove more precisely the value of rest. A rheumatic heart may (1) grow in size normally, (2) after a period of enlargement, remain stationary in size while the chest grows or (3) enlarge progressively. If adequate rest has been provided during the acute phase, in most cases the heart will not enlarge progressively. However, cardiac breakdown is not due to overexertion but to reinfection (Watkins [1881]). Unnecessary, anxious long periods of rest will produce cardiac neurosis.[532, 999]

[To avoid this needless complication the War Department urged medical officers not to overdo in the matter of resting convalescent rheumatic soldiers but to encourage the rheumatic soldiers to resume graduated physical activity as soon as the active disease subsided. The War Department's memorandum thereon [1870] will be instructive to civilian physicians.—Ed.]

Salicylates. These remain the most valuable remedy and are almost specific for relieving symptoms. Differences of opinion exist as to the dosage required and as to the relative merits of oral or intravenous administration. This old controversy (Mendel, 1904) was recently reopened by Coburn [330] who reported a method for determining concentration of salicylates in blood and expressed his belief that acute rheumatic fever could be rapidly suppressed if, by the intravenous administration of salicylates, concentrations were maintained at about 35 mg. per 100 c.c. of plasma. In 38 patients so treated "valvular heart disease" did not develop but in 21 (33 per cent) of 63 patients given orally smaller doses of salicylates signs of "heart disease" developed.

Preliminary approval of the intravenous use of large doses to obtain high blood levels was given by some,[650, 691, 999, 1055, 1195, 1969] but subsequent workers were not able to confirm the value of high blood levels.

No difference was noted in the effect on sedimentation rates, and the final percentages of patients who had cardiac damage were identical in all of three groups of patients of Warren, Higley and Coombs treated thus: small oral doses of salicylates sufficient to control symptoms in 88 patients; larger oral doses to maintain adequate levels in the plasma in 50 patients; large doses given intravenously by Coburn's technic. Similar disappointing experiences were reported by others.[269, 967, 1275, 1902, 1903] The intravenous use of large doses of salicylates and the maintenance of high blood levels did *not* give results superior to those from the oral use of standard doses. The former did not control or prevent recurrences, hasten the return of sedimentation rates to normal, hasten materially the subsidence of the acute phase of rheumatic fever, or prevent the development of carditis.

The effect of salicylates on enzymes and metabolic processes in animals was studied in detail (Lutwak-Mann). Certain notable changes in liver glycogen occurred. Urinary metabolites of sodium salicylate also were studied (Kapp and Coburn).

1. Toxicity of Salicylates. Besides having no advantage over the oral use, the intravenous use of salicylates was condemned as dangerous.[1195, 1591, 1874, 1903, 1969]

Even though plasma levels were the same, toxic reactions occurred six times as often in patients treated intravenously as in those treated orally by Warren, Higley and Coombs,[1874] but in most cases reactions were mild: nausea, occasional vomiting, tinnitus, colored vision. With the highest blood levels hyperventilation, acute maniacal delirium and pustular acne sometimes developed.

When large doses of salicylates were given orally to McEachern's [1195] patients,

discomfort (usually only mild nausea or tinnitus) developed in less than 25 per cent but when salicylates were given intravenously, marked symptoms developed in nearly all 37 cases. These consisted of vomiting, shaking chills in 10 cases and in six cases acute psychosis, incoherent speech, disorientation, rapid pulse, acute air hunger. One death occurred.

Other fatal reactions were reported. Salicylate toxicity produces respiratory alkalosis.[371] Five of 10 children with salicylate poisoning died from circulatory or respiratory failure.[782] Fatal salicylate poisoning with hemorrhagic manifestations was reported.[44, 506, 1814] The doses of salicylates used in rheumatic fever lower the prothrombin content of blood but not seriously; the reduced prothrombin time can be corrected readily by the use of vitamin K.[269, 546, 1232, 1433, 1593] The use of vitamin C notably improved one patient's tolerance to salicylates.

2. Treatment of Salicylate Poisoning. Large quantities of lactate-Ringer's solution and dextrose were given intravenously for several days (Hartmann).[782] If sodium bicarbonate is given in conjunction with salicylates the concentrations of plasma salicylates may be lowered.[907, 1642, 1647, 1874]

Sulfonamides. These are of no value during acute rheumatic fever but are apparently of great value in the chemoprophylaxis of the disease as will be discussed later.

Penicillin. The same may be said of penicillin which is of no value during acute rheumatic fever; indeed according to some observers penicillin given at that time aggravates the disease.[578, 1432, 1828, 1884]

[Penicillin may be useful in controlling certain complications due to hemolytic streptococci; for example, acute otitis media.—Ed.]

Other Drugs. Carditis, toxicity and relapses occurred much less frequently when Gubner and Szucs [711] used a succinate compound (calcium double salt of benzoic acid and succinic acid benzol esters) rather than salicylates. To control nervous instability the use of sedatives such as phenobarbital was recommended for children with active and subacute rheumatic fever or chorea (Hubble).

Antireticulocytotoxic Serum (Bogomoletz' A.C.B. Serum"). Claims were made by Bogomoletz [168, 169] and Strazhesko that "rheumatism" was relieved by injecting subcutaneously minute amounts of antireticulocytotoxic serum into patients.

The serum was usually obtained from rabbits immunized against human reticuloendothelial tissue cells. It is not clear what type or types of "rheumatism" were treated. Bogomoletz [168, 169] claimed that "in cases of acute arthritis it is a quick and certain cure, but when there is endocarditis, application of the serum has a bad effect." Strazhesko stated: "In chronic rheumatism (chronic arthritis and endocarditis) the serum should not be used."

This serum was investigated for the British Empire Rheumatism Council by Bach.[48] Among the various rheumatic patients treated were two with rheumatic fever. Results in these cases were negative. The Council did not recommend its use. When informed of Bach's work, Bogomoletz [168, 169] is said [1951] to have stated: "The serum is suitable for the cure of rheumatism only in the acute phase of the illness." [Which leaves us as confused as before.—Ed.]

Spinal Fluid "Pumping" (Speransky). Spinal fluid "pumping" in the treatment of rheumatic fever was approved by the Gillmans who espoused the theories of Speransky.[653]

The rationale and technic were explained thus: Antibodies in the blood stream fail to pass into the nervous system. To cause antibodies to pass across the hematoencephalic barrier into the brain and spinal cord and thus offer protection even against the intrathecal injection of toxins, Speransky developed spinal fluid "pumping"—the repeated withdrawal and introduction of 10 c.c. of cerebrospinal fluid 20 times in 40 minutes. By increasing the permeability of the hematoencephalic barrier, this pumping presumably allowed antibodies (or medicinal agents such as salicylates) to pass into the central nervous system. Pumping also provided "a specific type of nerve irritation" which, under certain circumstances, was said to have remarkable therapeutic value. Pumping, generally in connection with salicylate therapy (for one or two days before and after pumping), was used by the Gillmans [653] to treat 100 patients: of 52 "treated during their first acute attack of rheumatic fever," 36 (72 per cent) "recovered completely." Of 33 patients with recurrent attacks 23 (70 per cent) "had no further attacks." Of 127 patients with rheumatic fever treated by salicylates alone (without pumping) only 48 per cent recovered completely. Because the pumping did not produce significant increases in the salicylate content of spinal fluid and because pumping alone was no less effective, the results were presumably not related to salicylates.

Untoward reactions sometimes occurred: severe headache, vomiting, fever. Death from multiple cerebral petechial hemorrhages occurred three days after a second pumping in a hypertensive patient with rheumatic fever; death was considered possibly from hypoprothrombinemia from salicylate poisoning rather than from the pumping. [It was not proved that the supposedly beneficial effects resulted from the pumping rather than from salicylates or from spontaneous remissions which commonly occur. We do not recommend spinal pumping.—Ed.]

Special Treatment for the Heart. To provide a superior form of "cardiac rest" patients with acute rheumatic fever and carditis were treated for long periods in oxygen chambers.[1527] Final results were not given. Edstrom [510] in Sweden reconstructed a hospital ward into a climatic laboratory where the temperature was kept constantly at 32° C. and the relative humidity between 35 and 40 per cent. Of seven rheumatic patients living in this "microclimate," six became free of symptoms and capable of work.

The effects of various drugs on 44 children with congestive heart failure and active rheumatic fever were studied (Walsh and Sprague). Xanthine diuretics were of greatest value. Digitalis was of value but it was necessary to use great care in its administration as three patients who showed toxic effects from digitalis died suddenly. Mercurial diuretics were effective. But if digitalis was given immediately preceding the diuretic, digitalis toxicity could be induced in connection with the loss of fluid.

The problem of cardiac neurosis and the need for adequate mental hygiene was stressed (Ershler [532]; Massell and Jones [1174]; Robertson, Schmidt and Feiring; Sieracki).

Prevention of Rheumatic Fever

By Individual Sulfonamide Prophylaxis. The prophylactic use of sulfonamides for the prevention of recurrent rheumatic fever has been studied since 1936 when Thomas and her co-workers, and Coburn and Moore began their work. From 1941 through 1945, 10 different groups of investigators published results of controlled studies.[24, 309, 332, 473, 549, 752, 753, 1048, 1049, 1051, 1222, 1377, 1734, 1783, 1784, 1785] These studies have been summarized.[1502, 1630] Small doses of sulfonamides were administered daily to rheumatic patients (not in the active stage of rheumatic

fever) during fall and winter months. Results of treatment and the course of the disease among treated patients were compared with those of an almost equal number of patients who received no sulfonamides. Total results published through 1945 are summarized in table 2.

Among rheumatic patients protected by sulfonamides more than 1,037 seasons only 22 acute exacerbations occurred, an incidence of 2.2 per cent; only three patients died from rheumatic fever. But among rheumatic patients who received no sulfonamides during 1,340 seasons 183 acute attacks (an incidence of 13.7 per cent) and five deaths (to date) from rheumatic fever occurred. In other words, among the patients not protected by sulfonamides there were six times as many acute recurrences and almost twice as many deaths as among those who received sulfonamide prophylaxis.

[In our opinion these results are most impressive and we believe that sulfonamide prophylaxis appears to represent an important medical advance.—Ed.]

Sulfanilamide was generally used: 0.5 to 1 gm. daily for children; 1 to 2 gm. for adults. [Thomas now recommends for adults one daily morning dose of 1 gm.—Ed.] Consensus was that administration should be begun when the active rheumatic attack has subsided, preferably before the patient leaves the hospital so that studies on possible toxicity can be done before the child returns home. Usually the drug was given only during the fall and winter months, or from October to June. But others considered it best to administer it throughout the year.

Toxic reactions were reported variously as "few," "rare, generally mild," "in 10 per cent generally mild." But toxic reactions occurred in more than 30 per cent of the cases of Stowell and Button,[1734] and one death resulted from agranulocytosis in a 12 year old boy who unfortunately neglected to report for appropriate treatment until 60 hours after the onset of symptoms. Most of the toxic reactions, however, consisted of relatively mild rashes, fever, leukopenia, or mild hemolytic anemia which cleared promptly when use of the drug was stopped. The use of sulfadiazine or sulfamerazine may reduce markedly the incidence of toxicity.

Short-time prophylaxis was used by Glazebrook and Thomson [658] who gave certain school boys with acute tonsillitis 15 to 20 gm. of sulfanilamide for four or five days, none to others. Of 16 cases of acute rheumatic fever which developed later 12 occurred in patients not so treated, only four in those who had received sulfonamide.

By Mass Sulfonamide Prophylaxis. This was first used by the armed services in World War II. Probably more than 1,000,000 men at some time during the war received sulfonamide prophylaxis, generally with sulfadiazine, usually 1 gm. daily. These studies were initiated by the Navy and by the Army Air Forces. The effects of mass prophylaxis on the occurrence of rheumatic fever, meningococcic meningitis, scarlet fever, other hemolytic streptococcic diseases, and respiratory diseases were observed. The incidence of these diseases in a treated group of several thousand persons was compared to that in untreated controls.[83, 331, 852, 855, 1873, 1943] The incidences of respiratory and streptococcic diseases in the treated groups decreased from 50 to 85 per cent. A reduction in rheumatic fever paralleled that in respiratory diseases (Coburn [331]; Holbrook [855]). At one station where sulfadiazine prophylaxis was instituted, the rheumatic fever rate fell from 87 to 0 per 1,000 in four weeks (Carter). Similarly complete control of a scarlet fever epidemic and marked reduction in respiratory diseases were reported (Watson, Schwentker, Fetherston and Rothbard).

TABLE II

Summary of Consolidated Reports on Sulfonamide Prophylaxis of Rheumatic Attacks

Investigator	Year	Patients Treated		Untreated Controls		Toxic Reactions
		Person-seasons	Rheumatic Attacks (Definite)	Person-seasons	Rheumatic Attacks (Definite)	
Thomas, France and Reichsman[1783, 1784, 1785]	1939 1941 1942 1944	114	4	150	21	Rare, generally mild
Coburn and Moore[332]	1939 1940 1941	184	1	163 100	37 13	In 10%, generally mild
Stowell and Button[1734]	1941	46	0	14	2	In more than 30%, one fatal
Hansen, Platou, Dwan and Pennoyer[753, 1377]	1942 1944	131	7	58	27	Rare
Kuttner and Reyersbach[1048, 1049, 1051]	1943 1945	108	1	104	23	Had to stop treatment in 15%
Chandler and Taussig[309]	1943	41	0	41	5	Few, mild
Dodge, Baldwin and Weber[473]	1943	170*	6	138	19	Mild and rare
Messeloff and Robbins[1222]	1943	50	3	60	3	Few, mild
Feldt[549]	1944	89	0	42	3	Infrequent and unimportant
Anderson[24]	1945	104	0	470	30	Occasional, mild
Total		1,037	22 = 2.2%	1,340	183 = 13.7%	

* Dodge, Baldwin and Weber studied 181 person-seasons but 11 had already been reported by Kuttner and Reyersbach; hence the latter are subtracted for this consolidated reoprt.

[From these and other studies it now seems probable that mass sulfonamide prophylaxis can eliminate meningococcic meningitis, greatly reduce scarlet fever and other streptococcic diseases, and reduce the hospital and dispensary admission rates for respiratory diseases and rheumatic fever, provided only that the bacterial organism is sulfonamide sensitive.—Ed.]

Toxic reactions during this mass sulfonamide prophylaxis were in general mild and infrequent. Among 40,000 persons receiving sulfadiazine studied by Holbrook,[855] only 0.12 per cent had reactions of any type and only 13 persons (0.03 per cent) lost time from duty. There were no deaths. Coburn [331] reported mild reactions (evanescent rashes) in 0.5 per cent of 30,000 troops receiving prophylaxis. More serious reactions occurred about once in each 10,000 cases, incidence of 0.01 per cent. In treating 25,000 persons Lee observed mild reactions in 0.5 per cent, more serious reactions in 0.036 per cent, no deaths.

The problem of sulfonamide-resistant strains of streptococci developing during prophylaxis has not been completely settled. During the individual prophylaxis of the several hundred rheumatic persons over several years no resistant strains developed. The only epidemic in the Army Air Forces caused by sulfonamide-resistant streptococci was introduced to Keesler Field by an inductee from southern California. Sulfonamide prophylaxis had not been used at Keesler Field and so far as the inductee knew he had not received sulfonamide. This Group A, Type 17 streptococcic epidemic did not respond to sulfadiazine prophylactically or therapeutically and produced more than 1,000 cases of streptococcic sore throat, some scarlet fever, and other streptococcic sequelae.[2, 1251] The Navy had similar experiences with epidemics of sulfonamide-resistant streptococcic diseases. Penicillin was effective in all reported sulfonamide-resistant streptococcic epidemics. The method by which streptococci become resistant is not as yet clear. The work of Demerec suggests that resistance is not induced by the action of the drug on the bacteria but that sulfonamide prophylaxis suppresses or kills off the sensitive organisms, thus "leaving the field" to the occasional sulfonamide-resistant organism.

By Penicillin. The possible use of penicillin for such prophylaxis was mentioned hopefully but no precise data appeared in the literature under review.

By Climate. The marked differences in the incidence of acute rheumatic fever and in the postmortem incidences of rheumatic carditis in various geographic regions has suggested that certain climates may possess considerable prophylactic value. During the war the Army, Navy, and Army Air Forces designated special hospitals located in areas of low incidence to be convalescent centers for several thousand soldiers recovering from rheumatic fever. No final report on recurrences in this group has been published as yet but a preliminary report on the first thousand patients so transferred by the Army Air Forces was made: no recurrences occurred among those remaining in these areas of low incidence (Holbrook and van Ravenswaay [856]). Among 376 other rheumatic patients observed by Miller [1243] for six months in such a convalescent hospital only two had acute exacerbations while at the hospital; five other patients who had been home on furlough to an area of high incidence returned to the hospital with recurrent attacks.

Initial attacks of rheumatic fever are occasionally seen among natives of regions of low incidence, but *recurrent* attacks are rare among residents or among rheumatic patients coming to the area.[452, 845, 1602] However, the prophylactic effect of climate can be a solution for very few of the large numbers of rheumatic patients who require protection from recurrences (Boyer).

By Diets and Vitamins. When two boiled eggs and two frozen egg yolks were added by Coburn and Moore [334] to the daily diet of 43 rheumatic children, no recurrences developed even though hemolytic streptococcic infections occurred.

[If this interesting observation can be confirmed it will be most important.—Ed.] "The importance of vitamins A and D, milk, protein, and the value of sun bathing cannot be overemphasized" in the treatment and prevention of rheumatic fever (Peete). Rinehart suggested that vitamin C may have a prophylactic effect against rheumatic attacks. Vitamin C was reported to be specific for nosebleeds occurring in rheumatic fever (Camp and Galvin) and for reducing sensitivity to salicylates so that larger doses may be taken (Pelner).[1360]

By Vaccines and Serums. Since 1933 Wasson and Brown [1877, 1878] have studied the prophylactic effect of streptococcic vaccination. Between September, 1940, and June, 1942, 80 ambulatory children with rheumatic carditis received an average of six intradermal inoculations of tannic acid precipitated toxin of the N.Y.5 strain of hemolytic streptococcus. Only one recurrence was suspected. Of a control group of 62 similar patients 11 had recurrences with three deaths. [These results are impressive but must be confirmed by others before a final opinion thereon can be formed.—Ed.]

By Salicylates. In general salicylates given between attacks have not prevented rheumatic recurrences. But when salicylates were given to rheumatic children at the onset of infections of the upper respiratory tract, some of the (otherwise impending) exacerbations have apparently been prevented (Schlesinger, 1938). Coburn and Moore [333] administered daily 4 to 6 gm. of sodium salicylate to rheumatic patients as soon as acute pharyngitis started. If throat cultures revealed hemolytic streptococci, salicylates were given for four weeks; otherwise the use of the drug was stopped. Of 47 rheumatic patients having hemolytic streptococcic pharyngitis so treated rheumatic fever developed in only one (2 per cent). Among 139 untreated controls, 57 (41 per cent) had rheumatic fever.

[With this plan salicylates are given at a time when sulfonamides are powerless to prevent recurrences; that is, between the onset of the acute hemolytic streptococcic infection and the usual time for the appearance of the rheumatic attack. If this work can be confirmed, this method may provide a needed supplement to sulfonamide prophylaxis.—Ed.]

By Control of Air-borne Infection. During the war well-controlled studies were made on the effect of oiling floors and bedding in barracks.[630, 1473] A reduction in respiratory infections resulted. Installation of ultraviolet lights in classrooms, barracks, and hospital wards [1537] also resulted in a reduction of air-borne diseases. Several germicidal vapors (aerosols) gave promising results.[233, 757, 1417] [These methods of controlling air-borne infections are not yet entirely practical but offer promise for the future when certain technical difficulties can be overcome.—Ed.]

By Community Responsibility and Public Health Services. More than 30 papers recently pointed to the necessity of mobilizing communities against rheumatic fever. Public health measures like those which have been so successful against tuberculosis are needed to control rheumatic fever. The following needs were stressed: adoption of standards for diagnosis and treatment; promotion of facilities for care; coördination and financing of research, and programs of professional and public health education.[39, 87, 213, 805, 887, 1158, 1191, 1347, 1350, 1463, 1519, 1682, 1918] The United States Children's Bureau recently adopted a program for children with rheumatic carditis.[861, 885]

[In December, 1943, the American Council on Rheumatic Fever was formed, sponsored by the American Heart Association. Representatives from medical and lay organizations make up its membership. The Council's objectives, briefly, are to foster the extension of

public and private programs for treatment, to secure aid for special studies on rheumatic fever and to promote public and professional education.—Ed.]

Sydenham's Chorea

Clinical Data. This disease which affects children and young adults, more commonly girls, was considered one of the major manifestations of rheumatic fever (Bennett and Hoekstra). In 25 per cent of rheumatic children chorea is the first sign of rheumatic fever; in another 25 per cent chorea develops some time in the evolution of their rheumatism; some children with chorea never have any (other) rheumatic episode (Hubble).

Chorea is rare in the tropics; one case in a Negro boy from Miami was noted (Saslaw). Electroencephalograms of 23 children with Sydenham's chorea were studied: The tracings were not specific but revealed dysrhythmias like those found in epileptics or in cases of head injuries (Usher and Jasper).

In chorea mitral valvulitis occurs often; aortic valvulitis rarely: six cases of the latter have been reported previously; a seventh was added (Berk).

Treatment. Infectious chorea is a self-limited disease lasting from one to six months, often with recurring attacks. Criteria of effective therapy are (1) whether the duration of the disease has been shortened and (2) whether rheumatic heart disease has been prevented. Artificial fever therapy was considered almost specific. In 17 cases typhoid-paratyphoid vaccine reactions were used to produce temperatures of 104°–106° F. for two hours daily on eight consecutive days (Bennett and Hoekstra). E. L. Bauer [88] treated 300 patients by such febrile reactions with good results. The presence of acute arthritis, myocarditis or endocarditis did not increase the hazard of treatment. Chorea rarely recurred after a full course of protein shock therapy had been given (Tucker).

Drugs, including salicylates, were of little value. Mental and physical rest and efficient nursing were considered important.[1818] Three patients were treated successfully with vitamin B_6: chorea may be related to a vitamin deficiency, especially of the B_6 factor (Schwartzman). Several patients were treated with small daily doses of insulin: preliminary results were "remarkably good"; relapses were not noted (Eitzen).[515]

Erythema Nodosum

Formerly considered a specific disease chiefly if not always related to rheumatic fever, erythema nodosum is now regarded as a nonspecific reaction to a variety of infections or toxic agents, chiefly tuberculous and streptococcic infections,[588] perhaps less commonly to sulfonamides, coccidioidomycosis and sarcoidosis. In 74 per cent of 27 cases of erythema nodosum among children tuberculin reactions were positive, but among 325 consecutive cases of calcified pulmonary tuberculosis there were only three cases of erythema nodosum.[1103] Erythema nodosum affected only 10 of 1,000 patients with acute rheumatism (Perry).

New cases were discussed.[588, 985, 986, 1103, 1382] Females were affected three times as often as males. A severe type was noted in middle-aged women. The disease appears most often in April and May, rarely in summer and fall. "Erythema nodosum in adults might well be divided into two groups, those with and those without visceral manifestations." Among the 37 cases reported by Kerley

sarcoidosis was exhibited in those in which visceral manifestations were present. Erythema nodosum sarcoidosis in Europe and erythema nodosum coccidioidomycosis ("valley fever"; "valley rheumatism") in California are closely related if not the same disease (Kerley [985, 986]; Perry [1382]).

Chronic Arthritis: The Two Common Types

No nomenclature is acceptable to all, but the English classification designating the two common types as "rheumatoid arthritis" (synonyms: chronic infectious, atrophic, proliferative) and "osteoarthritis" (synonyms: senescent, hypertrophic, degenerative), although neither adequate nor descriptive, is the least confusing.[969] These terms, adopted by the American Rheumatism Association, are now in common usage in this country.

Rheumatoid Arthritis

Social and Economic Importance. Because rheumatoid arthritis does not occupy a prominent place in mortality statistics, its importance is woefully underestimated (Eiman). Yet this greatest crippler of man strikes persons in their most productive years (Margolis). The invalid's burden usually must be shouldered by the family, which more often than not is in poor financial circumstances. Adequate facilities for hospital or institutional care do not exist in any country.[1747] In the United States free beds for such patients do not number more than 200, whereas, there are more than 100,000 free beds for tuberculous patients.[1972] All in all "the great majority are not well looked after" (Sundelin).

Incidence. Morbidity statistics of the insured population of Scotland would indicate that rheumatoid arthritis is a "relatively infrequent affection" (Halliday [747]) in that country. Only 330 cases were reported out of a total of 378,207 instances of incapacity, an incidence of less than 0.1 per cent. This figure may be underestimated as many cases of rheumatoid arthritis probably "were hidden under the vague term of rheumatism." Of about 4,500 "rheumatic patients" seen annually by rheumatologists at the Mayo Clinic, 35 per cent have rheumatoid arthritis (Hench).[813] [This relative incidence, approximately a third, is found in most large arthritis clinics and prevailed also at the two centers for chronic rheumatic diseases of the United States Army (Hench and Boland).—Ed.] The over-all incidence of rheumatoid arthritis in the armed forces cannot be accurately calculated. Many, but by no means all, gravitated to army general hospitals and many were later sent to special rheumatism centers. Boland and Corr found that 12.4 per cent of 450 consecutive admissions for arthritis and allied conditions at an army general hospital were for peripheral rheumatoid arthritis (peripheral and spinal disease combined were responsible for approximately 20 per cent). For 79 per cent of 105 soldiers with arthritis studied by Wallace at another army general hospital the diagnosis was rheumatoid arthritis. [This incidence appears to be inordinately high and is not comparable to that reported from other army general hospitals. Was such a diagnosis often made for convenience in obtaining hospitalization?—Ed.] The incidence in British military hospitals was less: Savage [1541] found rheumatoid arthritis in only 1.85 per cent of 270 soldiers admitted for rheumatic diseases (incidence for peripheral and spinal disease combined was 7 per cent). At No. 3 General Hospital (British) rheumatoid arthritis was diagnosed in 6 per cent and fibrositis in 70 per cent of the first 100 cases of rheumatism (Copeman [376]). Rheumatoid arthritis was a major cause for evacuation of American soldiers from North Africa; such cases outnumbered rheumatic fever, rheumatic heart disease and pul-

monary tuberculosis as non-neuropsychiatric causes for evacuation and were exceeded only by cases of asthma, peptic ulcer and nonulcerous dyspepsia (Short [1599]).

That rheumatoid arthritis is a disease of temperate climate was noted again,[181, 434, 510, 968] but no new data regarding climatic incidence appeared. Cecil [305] remarked that victims of rheumatoid arthritis, "like its first cousin rheumatic fever," predominantly belonged to the poorer classes.

General Clinical Data. Detailed anthropometric studies, comparing body builds of rheumatoid and osteoarthritic patients, were conducted (Seltzer [1575, 1576]). Patients with rheumatoid arthritis were not as definitely linear as many clinicians had formerly stressed. The osteoarthritic groups were more distinctive and were highly pyknic showing strong laterality, stocky builds, big bones, big muscles. The average age at the time of onset of rheumatoid arthritis in 388 cases studied by Sclater was 40 years; the onset in 73 per cent of the males and in 66 per cent of the females was between the ages of 25 and 54 years. The ratio of females to males affected was 2.3:1. Kinsella thought that, when the disease began after the age of 50 years, the clinical pattern differed, being characterized by (1) more abrupt onsets, (2) "hot swellings," (3) more stormy and rapidly fluctuating courses, (4) more equal sex distribution, and (5) better prognosis.

In a civilian series initial involvement of fingers was more common in females (38 per cent) than in males (26 per cent) (Sclater). Boland noted that joints of lower extremities were the first affected in 70 per cent of soldiers; metatarsophalangeal and interphalangeal joints of feet were involved in 41 per cent of cases, while the corresponding joints of fingers were affected in only 10 per cent. Such figures suggest that joint trauma plays a part in initial localization (Bach [46]).

The usual prodromal symptoms and typical clinical pattern were reviewed.[171, 567, 1094, 1157, 1599, 1968] During the "prearthritic stage" rheumatoid arthritis may easily be confused with such generalized diseases as thyrotoxicosis, psychoneurosis or tuberculosis (Borman; Ropes and Bauer). Typical advanced rheumatoid arthritis, as described in most textbooks, offers little difficulty in diagnosis.[1493, 1494] But so-called "atypical" cases occur so frequently that it may rightly be questioned whether the clinical pattern of "insidious onset, slow progressive course and symmetrical joint involvement" should be labeled as usual or typical. Examples of atypical onsets and atypical early clinical courses, as observed by Ropes and Bauer, included: (1) asymmetrical involvement, often a monarthritis; (2) sudden febrile onsets precipitated by acute infection and accompanied by skin rash and migratory joint involvement; (3) bouts of arthritis precipitated by respiratory or other infections and not followed by permanent articular residues; (4) febrile onsets resembling rheumatic fever [these were common among soldiers.—Ed.]; (5) transient swellings affecting one joint and then another resembling the "palindromic syndrome"; (6) onset consisting of recurrent joint and muscle aching and stiffness with qualitative characteristics of so-called "primary fibrositis." According to Ropes and Bauer most patients with so-called fibrositis actually have mild rheumatoid arthritis, although often the diagnosis cannot be made until after long periods of observation. Most patients with "chronic synovitis" and "intermittent hydrarthrosis" eventually turn out to have rheumatoid arthritis (Ghormley and Cameron).

Minor roentgenographic deviations in the gastrointestinal tract (ptosis, dilatation and hypotonicity of gall-bladder, stomach, small intestine and colon) were often found in cases of arthritis, including rheumatoid arthritis.[1366, 1679]

Rheumatoid Arthritis: Special Clinical Features

Effect of Hepatitis. Complete or partial remissions, though temporary, may result when hepatitis or biliary obstruction of a degree sufficient to produce icterus develops in cases of rheumatoid arthritis. Subsidence of objective manifestations may be striking and demonstrates that the disease is potentially reversible. Two more such instances were noted.[1164, 1978] Attempts made to imitate this phenomenon experimentally by injecting bile salts and bilirubin intravenously failed.[1f] But Gardner, Stewarf and MacCallum produced hepatitis by inoculating rheumatoid patients with serum from patients with infective hepatitis. In 32 of 312 rheumatoid patients inoculated jaundice developed. During the incubation period no change in the arthritis was noted, but with the appearance of jaundice dramatic improvement was noted by 18 of the 32 patients (complete remission in 10, considerable improvement in eight). Disappearance of pain and swelling was quickly followed by increase in range of motion. "One patient whose fingers had been locked for two years was able to move them on the third day of jaundice. Then the swelling rapidly subsided, and by the sixth day she had full and painless movement of her fingers." The authors concluded that experimental hepatitis "provides an opportunity of producing a remission under controlled conditions and the possibility of analyzing the mechanism by which it is produced."

How hepatic damage produces its ameliorative effect remains unknown. In (non-jaundiced) patients with rheumatoid arthritis liver function, as gauged by hippuric acid and bromsulfalein tests, is generally normal (Robinson [1480]). No specific hepatic lesions have been found at necropsy (Rosenberg, Baggenstoss and Hench [54, 1500]). Snow and Hines studied the effect of obstructive jaundice on experimental arthritis in rats, produced by pleuropneumonia-like organisms. Ligation of the common bile duct prior to, or 20 hours after, inoculation with the organism delayed the onset of arthritis and diminished subsequent degrees of joint involvement. But ligation of the duct after the onset of arthritis did not affect the course of the disease. Arthritis induced by injection of hemolytic streptococci was not influenced by ligation of the bile duct. Snow and Hines suggested that the effect of obstructive jaundice on arthritis produced in rats by pleuropneumonia-like organisms was due to the solubility of these organisms in bile.

Effect of Pregnancy. Not every female with rheumatoid arthritis experiences relief when pregnant but the majority do (Aldred-Brown). A patient refractory to various forms of treatment including gold salts, was relieved completely by pregnancy (Flynn). The arthritis became asymptomatic at the fourth month of gestation, and the remission lasted two and one-half years; reactivation of the disease occurred six weeks after completion of a second pregnancy. In none of Sclater's 388 cases did rheumatoid arthritis first manifest itself during pregnancy. The mechanism of relief in pregnancy, as in hepatitis, remains a mystery.[883, 1480, 1561] Elevation of serum lipids, total cholesterol and phospholipids is common to both pregnancy and jaundice, but the blood in cases of rheu-

matoid arthritis is not deficient in these fractions.[101, 155] Because the disease may flare up after the puerperium, pregnancy was considered undesirable (Gill [652]).

Ocular Lesions. Uveitis was observed in two of 83 rheumatoid patients, and among 63 patients with uveitis, rheumatoid arthritis was noted twice, an incidence of 2.4 and 3.2 per cent respectively [128]; cultural studies from eye washings revealed no constant bacterial or filtrable agent. Two cases of band-shaped opacity of cornea associated with rheumatoid arthritis were reported: one in a 13 year old boy (Wong), another in a four year old girl (Kurnick). Nineteen of 24 additional children who had this rare corneal lesion also had juvenile rheumatoid arthritis. Its pathogenesis, like that of rheumatoid arthritis, is unknown. Smoleroff observed necroscleritis nodosa perforans (scleromalacia perforans, scleritis necroticans) in three patients with rheumatoid arthritis. In two other cases reported,[27, 557] pathologic changes in scleras consisted of multiple, disseminate and discrete areas of focal necrosis with superimposed subacute inflammatory reaction which developed into relatively large abscesses and finally were reduced to cavities (Fingerman and Andrus).

Cardiac Lesions. Although rheumatic cardiac lesions are found at necropsy in roughly 40 per cent of rheumatoids not nearly that many show evidences of cardiac disease in life, according to previous reports. But Feiring found clinical evidence of "carditis" in eight (29 per cent) of 27 patients with rheumatoid arthritis: "unequivocal auscultatory signs" in two (one had had rheumatic fever), roentgenographic evidence of progressive cardiac enlargement in one, and one or more electrocardiographic abnormalities in five (prolonged P–R interval in two, inverted T wave in two, bundle-branch block in two). Five rheumatoid patients studied by Logue and Hanson exhibited first degree heart block with P–R interval of 0.22 second or more. The disparity between the findings in life and at death indicated that the pathologic lesions are subclinical and not detectable before death (Hench [814]).

Amyloidosis. The association of amyloidosis and rheumatoid arthritis rarely occurs,[794, 1672, 1808] and then only in severe cases of long duration.[1170] Amyloid degeneration was found at necropsy in two of the 30 cases (7 per cent) of Rosenberg, Baggenstoss and Hench [54, 1500]; in 13 (21 per cent) of the 61 cases of Fingerman and Andrus.[27, 557] Fatal amyloidosis of kidneys, spleen and liver affected a rheumatoid patient.[1170]

Palmar Erythema. Palmar erythema may develop in severe or long-standing cases of rheumatoid arthritis and may be relieved by pregnancy or hepatitis (Perera). The peripheral vascular dilatation involves chiefly the eminences of the palms or fingertips, is sometimes called "liver palm," and is found also in other chronic diseases including pulmonary tuberculosis (Trostler), hepatic cirrhosis, and pregnancy (Lofgren). The cause is unknown but an abnormality in the metabolism of 17-ketosteroid hormones has been suggested (Bean [105, 106, 107]).

Pathologic Characteristics of Rheumatoid Arthritis

General. That rheumatoid arthritis is not solely a disease of joints but a systemic disease with widespread pathologic changes in various tissues and organs was emphasized by recent necropsy and biopsy studies. Particular interest was centered on lesions in heart, peripheral nerves and skeletal muscles.

Joints. Bayles [98] observed at necropsy in 23 cases essentially the same articular changes as the classical ones of Nichols and Richardson (1909), and Allison and

Ghormley (1931). Early changes in subsynovial tissues, as described by Bennett [122] consisted of diffuse lymphocytic and plasma cell infiltration with the frequent formation of lymphoid follicles. From biopsy studies, Steinberg [1701] concluded that no specific micropathologic changes exist in rheumatoid arthritis; variable pathologic pictures may be seen ranging "from one in which there is a polymorphonuclear infiltration to sections showing round cell infiltration, both perivascular and nonperivascular." Multiple osteochondral bodies developed in the synovia in one case of "mixed rheumatoid and degenerative arthritis." [1821]

Studies of joint innervation revealed no nerve fibers in cortical bone or in articular cartilage, but the joint capsule, periosteum and synovial membrane were richly supplied (Smyth and Freyberg [608, 1650]).

Bones. No new data appeared. Despite marked bone atrophy and cystic degeneration, fractures are infrequent complications of rheumatoid arthritis, and healing following fractures takes place normally (Baer). Large cysts formed above each hip joint in a case of Burt.[266]

Subcutaneous Nodules. The rheumatoid nodules of four patients consisted of focal fibrinoid degeneration and necrosis surrounded by a palisade-like radiate arrangement of fibroblasts, such as Collins (1937) described previously (Weber [1890, 1891]).

Peripheral Nerves. Widespread involvement of the peripheral nervous system in rheumatoid arthritis was demonstrated by Freund, Steiner, Leichtentritt and Price.[601, 602, 603] Lesions consisting of perineural nodules (nodular perineuritis) were irregularly distributed, not only in nerves of extremities but also in peripheral nerves unrelated to joints. The nodules consisted of an outer zone of lymphocytes with scattered plasma cells and an inner zone of polyhedral-shaped cells having large irregular nuclei, "not unlike epithelioid cells seen in other granulomatous tissue." Neuritic pains, paresthesia and trophic changes, common to the disease, might be attributed to such lesions. However, the sensory and muscular degenerative changes of rheumatoid arthritis cannot be entirely explained thereby because the nodules were always perineural, and endoneural lesions which would be expected to produce degeneration were not found.

Muscles. Freund, Steiner, Leichtentritt and Price [601, 604] also described "nodular polymyositis" (compact microscopic accumulations of lymphocytes, a few plasma cells, occasional epithelioid and eosinophilic cells) in specimens from 15 patients with rheumatoid arthritis. The disseminated nodules, found in biopsies taken at random (gastrocnemius, deltoid, pectoral, rectus abdominis, iliopsoas muscles), were discovered in every case and were considered specific lesions. In 196 control cases no such lesions were found. Associated changes in muscle fibers (irregularly distributed hydropic degeneration, edema, loss of striation, swelling or shrinkage, and atrophy) were found regularly. This degeneration was not related spatially to lesions of the synovia, periarticular structures, subcutaneous nodules or peripheral nerves, but was considered as an independent tissue reaction to the same unknown agent. Such widespread myositis (with coexisting nodular peripheral neuritis) offers an anatomico-pathologic basis for the muscle atrophy of rheumatoid arthritis which heretofore could not be explained on the basis of disuse alone. [These microscopic lesions in muscles notably resemble those in inflamed synovia and subchondral bone in rheumatoid arthritis. One of us, W. B., has found similar lesions in cases of disseminated lupus erythematosus and periarteritis nodosa.—Ed.]

Heart.—The hearts of 152 patients with rheumatoid arthritis were studied at necropsy.[27, 53, 54, 55, 98, 557, 1500, 1979] In a total of 66 (43 per cent) of these 152 cases, cardiac lesions indistinguishable from those of rheumatic fever were found; the incidence of such lesions varied from 26 to 66 per cent.

In 24 (80 per cent) of 30 cases studied by Rosenberg, Baggenstoss and Hench [54, 55, 1500] cardiac lesions were found. The lesions were "rheumatic" in 16 (53 per cent), "nonrheumatic" in eight (27 per cent) of the 30 cases. The rheumatic heart disease was the cause of death in seven of the 16 cases, although in none of these was there a history of rheumatic fever. Gross lesions were present in the mitral valve in 10, in the aortic valve in six, in the tricuspid valve in two, in the pericardium in six. These changes were subacute in three, chronic in eight, and inactive in five. Aschoff bodies were found in valves, pericardium or myocardium in all but two cases. Although pathologically identical, the lesions were considered less severe and less widespread than those seen in rheumatic fever.[55]

Rheumatic cardiac lesions were found by Bayles at necropsy in six (26 per cent) of 23 cases. In only one case was there a history of rheumatic fever; omitting this case, five of 22 (23 per cent) patients dying with rheumatoid arthritis had rheumatic cardiac changes at necropsy unexplained by a known previous attack of rheumatic fever. Similar rheumatic cardiac lesions were found by Fingerman and Andrus [27, 557] in 19 (31 per cent) of 61 cases of rheumatoid arthritis, in only two of which there was a history of rheumatic fever. Young and Schwedel found at necropsy cardiac lesions in 33 (87 per cent) of 38 cases of rheumatoid arthritis: the lesions were "rheumatic" in 25 (66 per cent), "nonspecific" in 8 (21 per cent) of the 38 cases. A history of rheumatic fever was noted in only three cases, of probable rheumatic fever in two others.

Various explanations were offered for these findings: (1) that rheumatoid arthritis and rheumatic fever are closely related, possibly identical diseases; (2) that the lesions found represented not "rheumatic carditis" (of rheumatic fever) but "rheumatoid carditis," which idea would necessitate a complete revision of thought about the supposed specificity of the lesions of rheumatic carditis; (3) that the patients actually had had two diseases, rheumatoid arthritis and rheumatic fever, the latter generally having been insidious and unsuspected in life because of the general absence of acute rheumatic polyarthritis.[814] None of these explanations are entirely satisfactory; certainly these incidences of rheumatic cardiac lesions among rheumatoids are much greater than those heretofore reported in ordinary necropsy studies on the general population. But according to Hall and Anderson the incidence of rheumatic stigmata in hearts studied at necropsy is much higher than has been supposed and such stigmata were found in 112 (about 90 per cent) of 124 hearts which by ordinary criteria would have been considered "nonrheumatic" (free of gross valvular lesions; no clinical evidence of rheumatic infection or valvular disease in life). Minimal thickening of mitral valve leaflets was observed 74 times (66 per cent) and the chordae of the mitral valve were thickened in 42 cases (37.5 per cent). Characteristic stigmata (arteritis, fibrinoid change, elastic tissue alterations, Aschoff bodies, infiltration histiocytes) were abundantly present. Aschoff bodies were found in 33 cases (29.5 per cent) and "Aschoff-like collections" in an additional 34 (30 per cent). This suggests that minimal subclinical cardiac lesions of rheumatic fever are widespread throughout the general population. [Most of these lesions were microscopic; most of those in the rheumatoid patients were associated with gross changes.—Ed.]

Other Organs. Baggenstoss, Rosenberg and Hench [54, 1500] were unable to demonstrate lesions pathognomonic of rheumatoid arthritis in other visceral organs. Fibrous adhesions between visceral and parietal pleura were present in 22 of 30 cases, but no relationship between the healed pleuritis and rheumatoid arthritis was established. In

a high (63) percentage of their 30 cases evidence of glomerular endothelial proliferation was present; perhaps the agent responsible for rheumatoid arthritis is also responsible for a low-grade, essentially subclinical glomerulitis. Moderate hypertrophy of lymph nodes, due to nonspecific hyperplasia of endothelial cells both within sinuses and within follicles, was found in eight cases. Coincidental lesions, apparently unrelated to rheumatoid arthritis, in gall-bladder, liver, gastrointestinal tract, spleen, pancreas, adrenals, thyroid, prostate and blood vessels occurred with about the same frequency as in routine necropsy cases.

Causes of Death. Three postmortem series included data thereon.[98, 557, 1500] Pulmonary complications, not related directly to rheumatoid arthritis, led the lists: miscellaneous pulmonary conditions (pulmonary embolism, bronchiectasis, bronchopneumonia, fat embolism, postoperative atelectasis and so on) were causes in 11 of 30 cases studied by Rosenberg, Baggenstoss and Hench [1500] and in five of Bayles' 23 cases. Cardiac causes were second in frequency; in nine (30 per cent) of Rosenberg, Baggenstoss and Hench's [1500] cases (rheumatic heart disease in seven, nonrheumatic coronary thrombosis in one, myocardial degeneration with decompensation of unknown cause in one); in four (17 per cent) of Bayles' cases (bacterial endocarditis in three, aortic stenosis with failure in one). Renal lesions caused death in three cases of each series. The remaining patients died of miscellaneous causes. The causes of death in the 61 cases of Fingerman and Andrus were: bronchopneumonia in 24, septicemia and pyemia in nine, lobar pneumonia in eight, tuberculosis in seven, carcinoma in three, amyloid disease in three, cardiac decompensation in three and uremia in two. [Not stated in two cases.—Ed.]

Laboratory Data in Rheumatoid Arthritis

Roentgenograms. The usual abnormalities were reviewed.[1022, 1754, 1995] Roentgenographic alterations often are absent in early cases [1599]: only 25 per cent of Short's patients,[1599] observed in an overseas general hospital, demonstrated roentgenographic changes; these usually were of varying degrees of bony atrophy. A common mistake is to rule out rheumatoid arthritis if roentgenograms are negative (Comroe [364]). Many different forms of arthritis exhibit the same basic alterations. Camp recognized the limitations of the roentgenologist in differentiating between the various types.

"If there is osteoporosis of the epiphyses and beginning narrowing of the cartilage space but no other abnormality of bony contour, the roentgenologist may recognize the changes as those of atrophic arthritis. There is probably some periarticular swelling. If there is a little marginal lipping of bone, instead of calling it atrophic and hypertrophic arthritis, he may discount the lipping and still call it atrophic arthritis. If there is considerable lipping with atrophy of bone and loss of cartilage space, what should he call it? Atrophic and hypertrophic arthritis? Clinically the patient should not have both, but roentgenologically he often has both. For example, an obese man with chronic atrophic (rheumatoid) arthritis will often have typical atrophic changes in the hand and ankle, but in the ankle he will also have considerable proliferation of bone. The roentgenologist cannot differentiate the atrophic changes seen in some cases of mild but moderately advanced gonorrheal arthritis from atrophic (rheumatoid) arthritis. If one has traumatic periarthritis (stiff, painful shoulder from injury, yet no alteration in cartilage or bone), it is not 'arthritis,' but if the arm is immobilized long enough in a sling or at his side the roentgenogram will reveal

osteoporosis in the shoulder joint. How can this be differentiated from early atrophic (rheumatoid) arthritis? In short many conditions may produce the same roentgenographic manifestations. The pathologic and roentgenographic response of joints in various diseases is too similar to permit dogmatic interpretation of the roentgenogram" (Camp).

Blood Counts and Plasma Proteins. Seventy-four per cent of 100 patients with rheumatoid arthritis had hemoglobin values of less than 80 per cent, presumably due to "toxemia" (Haden [727]), but Robinson [1480] concluded that the anemia is partially due to simple plasma dilution similar to that which occurs in pregnancy. Plasma protein values were consistently elevated in cases of severe rheumatoid arthritis (average of 4.11 gm. per kilogram of body weight versus a normal of 2.73 gm.), and the red cell volume was consistently reduced (29 mg. per kilogram of body weight versus a normal value of 34 mg.). The rise in plasma protein was thought to produce a hydremic effect and relative anemia from plasma dilution. The leukocyte picture is not characteristic [727]; leukopenia is frequent but occasionally mild polymorphonuclear leukocytosis occurs [1599]; the differential count is rarely altered and toxic granulation is not observed.[727]

Sedimentation Rate of Erythrocytes. Generally accepted [1725] as a useful index of the disease's activity, this test was considered by some as inaccurate.[1599, 1661, 1706] In 50 per cent of Short's [1599] early or mild cases rates were normal. Steinberg and Loewenstein observed patients with "hot swollen joints" whose rates were normal and patients with clinically inactive disease whose rates were increased. Some [1661] stated that careful clinical evaluation was much more dependable than the sedimentation rate both in diagnosis and in following the course of the disease. Fibrinogen and euglobulin contents of plasma tend to decrease as clinical improvement occurs, but the decrease in sedimentation rate and plasma proteins is not simultaneous.[1757] Usually fibrinogen returns to normal more slowly; the lag is interpreted as indicating continued activity despite a normal sedimentation rate.

Miscellaneous Tests. Retention of Congo red is not always diagnostic of amyloidosis; a rheumatoid patient retained 50 per cent of the dye (normal loss 20 to 30 per cent): amyloidosis was suspected but not found after death from hepatic cirrhosis.[1164] The Weltman reaction (coagulation of serum proteins in the presence of the electrolyte $CaCl_2$), was considered a sensitive indicator of activity in rheumatoid arthritis (Milles and Salt). In severe disease a shift to the left was usually found, and a shift to the right was thought to be a sign of good prognosis. But others[1706] considered that the test did not reflect the severity of the clinical picture, and Kling considered that the sedimentation rate of erythrocytes was a more accurate guide.

Liver function as measured by the hippuric acid test was subnormal in seven of 13 patients, a deficiency no greater than that found in "any other group of patients suffering from systemic disease." The test was not appreciably affected by gold therapy.[823] Amounts of acetylcholine esterase in blood serum of patients with "arthritis" (type not stated) were normal.[268] [They are low in pregnancy and severe hepatic damage, an interesting point in relation to the effect of pregnancy and hepatitis with jaundice on rheumatoid arthritis.—Ed.]

Mester [1223] described a test said to have special sensitivity for rheumatic patients. A leukocyte count is made, then an aqueous solution of salicylic acid is injected intradermally, and 30 minutes later another leukocyte count is made. According to Mester [1223] 98 per cent of rheumatic patients with acute, subacute or chronic disease but no controls showed a drop in the leukocyte count 30 minutes after the injection. However, Copeman and Stewart found the test to be of no aid in differentiating rheumatic from nonrheumatic diseases and warned against making a diagnosis based on its results; results were frequently negative in cases of frank rheumatic disease and

positive in a number of nonrheumatic conditions. Mester's test, employed by Green and Freyberg [696] in 20 cases of rheumatoid arthritis gave positive results in only five; they considered it grossly unreliable.

Films of small amounts (1 c.c.) of blood plasma on the surface of water were studied in cases of rheumatic disorders (Scull and Pemberton). The size of the film normally is about 550 sq. cm. and presumably is related to the concentration of plasma proteins. In cases of severe rheumatoid arthritis the films were found to be smaller (150 to 450 sq. cm.) than normal. Indoluria which does not occur in normal persons under normal conditions, was present consistently in patients with rheumatoid arthritis (Neuwirth [1293]). The mean plasma fibrinogen fraction was elevated in 53 cases of rheumatoid arthritis (mean of 520 mg. per 100 ml. of plasma versus a normal of 250 to 400 mg. per 100 ml.). Mester considered fibrinogen estimations to be of diagnostic aid.

Various tests on cerebrospinal fluid were made by Ludwig, Short and Bauer on 101 patients with rheumatoid arthritis. Fifty-nine had rheumatoid arthritis of peripheral joints and 42 had spondylitis with or without involvement of peripheral joints. Determined were the spinal fluid pressure, cell count, values for sugar, chlorides and protein, and the colloidal gold curves. The only significant abnormalities noted were increased concentrations of protein, abnormal colloidal gold reactions, or both. Concentrations of protein were increased (46 to 70 mg. per cent) in 6.8 per cent of the 59 patients with only peripheral joint involvement, in 28.6 per cent (47 to 105 mg. per cent) of the 42 with rheumatoid spondylitis, in 15.8 per cent of the total 101 patients. Colloidal gold reactions were abnormal in five (8.5 per cent) of the patients with peripheral joint involvement and in six (14.3 per cent) of those with spondylitis. These various abnormalities were considered to be the result of alterations in serum proteins and of an increased permeability of meninges caused by their proximity to inflamed articular tissue.

Etiology and Pathogenesis of Rheumatoid Arthritis

Factor of Infection. 1. General Comment. There is no proof that rheumatoid arthritis is an infective disease. Carefully conducted cultivations of blood and joint fluid have produced negative results. But many features suggest that infections play some part (Davidson [434]). These include: (1) clinical features of fatigue, weight loss, low-grade fever, lymphadenitis; (2) elevated sedimentation rate of erythrocytes and leukocyte counts; (3) frequent elevations in streptococcic agglutination and antistreptolysin titers; (4) frequent positive skin tests for streptococcic protein fractions. But, as Davidson pointed out, fever, leukocytosis, elevated sedimentation rate and other signs are not pathognomonic of infection; they occur in various diseases accepted as noninfectious, including gout (acute gouty arthritis). The finding of agglutinins, antistreptolysins and positive skin tests means only that the patient has been infected with streptococci, not that the arthritis is due to this organism.

2. Foci. "Infected focus" and "focal infection" are not synonymous terms (Shuster). An infected focus is a circumscribed region of tissue infected with pathologic organisms, whereas focal infection implies metastasis, from the infected foci, of bacteria or their toxins, capable of injuring contiguous or distant tissues. The mere presence of pathogenic bacteria in a focus does not necessarily imply the development of systemic infection.

The points for and against septic foci being of etiologic importance were summarized (Davidson [434]); those for this idea included the following: (1) streptococcic

infections of throat, tonsils or nasal sinuses may precede the initial or recurrent attacks; (2) dramatic improvement sometimes follows removal of a septic focus; (3) the pathologic and anatomic features of lymphoid tissue in tonsillar infection, sinus infection and root abscess suggest that toxic products can be absorbed into the circulation; (4) a temporary bacteremia may occur immediately after tonsillectomy or tooth extraction and after vigorous massage of the gums. Points against the idea included: (1) often no infected focus can be found; (2) usually when a focus has been extirpated, no dramatic results are produced; (3) many persons in perfect health or suffering from diseases other than rheumatoid arthritis may have septic foci in the same situations and of the same magnitude as patients suffering from rheumatoid arthritis.

In a study of 388 cases of rheumatoid arthritis Sclater obtained a history of some type of infection occurring within two months of the onset in 12 per cent of the males and in 21 per cent of the females; infected foci were present in 38 per cent. Pemberton [1370] stated that infected foci should be considered as one of the "drags" of the disease, not as a cause. But others [49, 1604] considered foci often to be chief etiologic factors.

In one series of 343 patients with rheumatoid arthritis, 57 per cent had infected foci somewhere [1971]; among 55 other patients, 65 per cent had some dental infection; 29 per cent had periapical infection.[1303] Perhaps dental infections are the result rather than the cause, the peridental tissues participating in the general lowered resistance. Neither hypercementosis nor pulp stones were thought to be related to arthritis,[1676] but severe periodontoclasia was considered a common focus.[527] Teeth showing periapical rarefaction in roentgenograms are considered infected and should be extracted [527, 690]; pulpless teeth without periapical rarefaction should be considered as questionable, not condemned, and roentgenograms made of them at intervals. But Goldberg [661] warned that cultures prove that roentgenograms are frequently unreliable in demonstrating root infection. Exercising rigid precautions in technic and culturing extracted apices of teeth in brain broth and soft brain-agar media, Stein [1699] obtained positive cultures from 15 per cent with living pulps (indicating a probable percentage of error in other figures), from 74 per cent of pulpless teeth with periapical radiolucent areas, from 71 per cent of pulpless teeth without periapical rarefaction.

The disease was ushered in by upper respiratory infections in 20 per cent of the cases of Boots and McCollem. Sclater found tonsils the most commonly infected focus; they were infected three times as often as teeth, 7.5 times as often as sinuses, about nine times as often as genitourinary tract and almost 100 times as often as gall-bladder. Evidence of chronic infection of viscera was disclosed in seven of Baggenstoss and Rosenberg's 30 cases (chronic cholecystitis in two; "moderate" chronic interstitial pancreatitis in three; chronic suppurative prostatitis in two). Bach [49] alone incriminated the colon and still spoke of it as a "focus of toxemia."

Green and Freyberg [695] studied the incidence of brucellosis in 25 cases of rheumatoid arthritis. Using agglutination tests, skin tests and phagocytic indexes as diagnostic criteria, no evidence of brucellosis was found in any case.

3. Cultures of Blood and Joints. Fraser [590] cultured in beef-heart infusion broth the blood of 61 patients with rheumatoid arthritis: no organisms were recovered in 58 (after 30 days' incubation); in three diphtheroid bacilli were isolated. Streptococci were never recovered. From five of 61 controls positive cultures were obtained: *Streptococcus viridans* in three, diphtheroid bacillus in two. Angevine, Rothbard and Cecil could find no significant organisms in blood, joint fluid, synovia or subcutaneous nodules. Pleuro-pneumonia-like organisms were cultured from prostatic secretion, urethra, cervix or vagina of seven patients with rheumatic complaints; two had rheumatoid arthritis (synovial fluid culture was made in one and found sterile), one had

"polyarticular swelling," and four had articular or muscular symptoms (Dienes and Smith [468]). That the joints and related involved structures remain sites of secondary metastatic foci after original septic foci have been removed was again suggested.[983]

4. Precipitins. No new data appeared.

5. Agglutinins. Patients with rheumatoid arthritis had agglutination titers of 1:160 or higher for hemolytic streptococci more often (58 per cent) than did normal controls (14 per cent) or patients with osteoarthritis (28 per cent) (Ferry and Hunt). The percentage of elevated titers for *Streptococcus viridans* was the same (20 per cent) in cases of rheumatoid and of osteoarthritis. The conclusion drawn was that elevated titers did not prove, but suggested, that hemolytic streptococci are etiologically related to rheumatoid arthritis.

6. Antistreptolysins and Antifibrinolysins. Increased titers for serum antistreptolysins are not characteristic of rheumatoid arthritis but in rheumatic fever they are usually present (Short and Bauer [1601]). Perry [1381] found increases in streptococcic antifibrinolysin titers in only two of 33 patients with peripheral rheumatoid arthritis and in one of eight patients with rheumatoid spondylitis. Bactericidal properties for hemolytic streptococci were detected more often in synovial fluids in cases of rheumatoid arthritis (two of nine cases) than of other articular disease (two of 28 cases) (DeGara).

Theory of Bacterial Allergy. Several favored this theory.[434, 662, 1392, 1561] Sclater wrote: "If infection is important it is probably not the frequency or the severity of the infection that is significant but perhaps the abnormal response of the patient to infection." Goldberg [662] considered such pathologic changes as perivascular lymphocytic and plasma cell infiltration in synovial villi suggestive of an allergic reaction. Davidson's concept [434] was that patients with rheumatoid arthritis have an abnormal immunologic response, the tissues being sensitive to bacterial antigens. Whereas, "the normal response to infection is the development of immunity, an abnormal response produces a state of allergy." He pictured bacterial antigens entering the circulation, coming in contact with fixed tissues in joints and provoking an allergic reaction "evidenced by an explosive discharge of histamine-like substance which produces dilation and increased permeability of capillaries," and hence, "swelling of soft tissues, heat and pain."

Virus Theory. No new data appeared.

Factor of Trauma. Although not the direct cause, trauma may at times act as the agent which precipitates the onset (Ryden). By lowering local resistance, major or minor injury to joints strongly influences the location of arthritic involvement (Kelchner; Lewis [1094]).

Factor of Circulatory Disturbance. The peripheral vascular responses of patients with rheumatoid arthritis follow a characteristic pattern, according to Naide, Sayen and Comroe.

The basal vascular tone was high and peripheral vessels were easily constricted (i.e., vasospastic type). This pattern was thought to account for the thin atrophic skin with cold clammy hands and feet, cutaneous pigmentation, causalgia, hyperesthesia, symptomatic improvement from vasodilating procedures and perhaps flare-ups of the disease after emotional upsets and exposure to cold. Rheumatoid arthritics were found to have been of the vasospastic type before the disease actually developed. Normally high vascular tone is more common in women than men and is most marked in fingers and toes; this may account for the sex incidence affecting females and the predilection for involvement of finger and toe joints. Steinbrocker and Samuels made oscillometric readings in 47 cases of rheumatoid arthritis: in 60 per cent vasospastic arterial disturbances were noted. Only 33 per cent of 71 patients with osteoarthritis showed similar findings. Entirely different results, however, were reported by Benatt and Taylor who, taking skin temperatures of finger tips and recording the response

to immersions in hot and cold water, found that patients with rheumatoid arthritis had normal responses; no specific type of functional vascular reaction could be detected. No evidence of increased vascular tone was elicited.

Factor of Altered Metabolism. Standard glucose tolerance tests, with simultaneous determinations of sugar in arterial and venous blood, were done in eight cases of rheumatoid arthritis.[26] Diminished tolerances for carbohydrates were found in all, which to Andrews and Muether indicated decrease in the glycogenic function of the liver rather than pancreatic dysfunction or circulatory stasis. Block and Murrell found no abnormalities in total sulfur, total nitrogen and amino acid contents or total serum proteins in rheumatoid arthritis. According to them, such negative findings invalidated any suggestions that an altered composition of total serum proteins in arthritic patients reflects disturbed sulfur metabolism. Total lipid, total cholesterol and phospholipid contents of the plasma were normal.[101, 155] Calcium and phosphorus metabolism studies were made in nine patients [1496]: in seven (78 per cent) the excretion of calcium in urine and feces was greater than normal, but phosphorus metabolism was essentially normal in all. The negative calcium balance was slight but definite (average excretion of 15.1 mg. per kilogram of body weight versus average normal excretion of 12.7 mg.) and was considered indicative of an increased rate of calcium metabolism. A definite correlation existed between the amount of decalcification noted roentgenographically and the rate of calcium excretion. Six of the nine patients with osseous atrophy had negative calcium balances averaging 0.61 gm. per day; three patients without atrophy had negative balances averaging 0.30 gm. One author [1567] vaguely discussed "multiple metabolic deviations" that supposedly characterize the "rheumatoid state."

Factor of Diet. Detailed analyses of diets used by 31 patients for a year before the onset of rheumatoid arthritis were made (Bayles, Richardson and Hall). The "pre-rheumatic" intake of calories, protein, fat, carbohydrates, vitamin A and its precursors, thiamine, riboflavin, vitamin C, calcium and iron was essentially the same as for nonarthritic persons living in North Atlantic states. Conclusion: "If a food deficiency contributes to the onset of rheumatoid arthritis, it must be caused by an increased total requirement rather than a deficiency in diet." One author [1822] considered allergy to various foods an important causal factor in arthritis. [No satisfactory supporting evidence was given.—Ed.]

Factor of Vitamin Deficiency. Lowered values for carotene pigments, carotene and xanthophyll as well as vitamin A itself have been reported previously in cases of rheumatoid arthritis (Race, 1937; Ellman, 1939) but no new data appeared. Mild states of vitamin B deficiency, manifested by mild dermatitis, sore mouth and red tongue, are seen at times when the disease is accompanied by marked anorexia and malnutrition (Freyberg [605]), but such deficiencies should be considered as complications, not causes of the disease. No striking differences were found in the riboflavin values of eight normal persons and of 56 patients with rheumatoid arthritis (Bradford and Coke). Most patients (62 per cent) with rheumatoid arthritis have abnormally low values for plasma ascorbic acid [605] but clinical scurvy is rare. Freyberg [605] found no relationship between the severity of the arthritis and the ascorbic acid content of blood, and although treatment with vitamin C corrected the deficiency, the course of the arthritis was unaffected. But Bradford [198] considered that some correlation existed between low vitamin C levels and excessive tiredness, tendency to bruising and gastric disturbances in patients with "rheumatic diseases."

Factor of "Intestinal Toxicosis." This almost forgotten theory still has disciples.[84, 600, 828]

Factor of Endocrine Abnormality. Although a few believe otherwise,[1138, 1282, 1372, 1732] there is no conclusive evidence that endocrine imbalance plays a part in the production of rheumatoid arthritis [1094, 1601]; the simultaneous occurrence of some form

of endocrine dysfunction is no more frequent than can be explained by chance (Davidson [434]). But Pemberton and Scull [1372] believed that both rheumatoid and osteoarthritis may be related to disturbances "of the neuroendocrine system as a whole and especially those of the pituitary gland." Sclater correlated the time of onset of rheumatoid arthritis with the cessation of menstruation in 132 females; in 19 (14 per cent) the disease began during menopause (a time latitude of two years before and two years following cessation of menstruation was allowed). This was considered a chance association; the conclusion was drawn that "menopause does not tend to precipitate the onset of rheumatoid arthritis." Low basal metabolic rates were found to be the rule in patients with any low-grade chronic disease. In 166 debilitated persons, including patients with "chronic arthritis," the mean metabolic rate was −8 per cent (Stiles [1726]).

Psychogenic Factor. The accelerated interest in psychosomatic medicine has extended to the field of rheumatic diseases. Opinions vary, however, as to what part psychogenic factors play in the etiology, predisposition, precipitation, and clinical course of rheumatoid arthritis. Some current views are: "Without implying that rheumatoid arthritis is of psychogenic origin, we do believe that the physician must recognize the fact that worry, grief and anxiety can be major contributory factors of this chronic disease" (Short and Bauer [1601]). "I am prepared to believe that an emotional crisis may predispose or precipitate arthritis in a patient whose body contains the fundamental bacterial or other causative agent of the disease, but I do not believe that without the latter the disease can be produced by psychic distress alone" (Hench [813]). "We hold no brief for the concept that organic joint disease, such as chronic rheumatoid arthritis, may be caused by psychic conflicts, per se" (Boland and Corr). "There is no evidence for a primary psychogenic cause; psychological elements are of importance not as causes of rheumatism but rather as sequels to it, often remaining latent until activated by a rheumatic attack" (Medical Advisory Committee on Chronic Rheumatic Diseases for Scotland [1215]). But Cecil [301, 306] stated that psychic factors were more important than infection in provoking the original symptoms or in bringing about relapses of rheumatoid arthritis.

Emotional factors were studied in 25 cases by Patterson, Craig, Waggoner and Freyberg and by Martin.[1161] About half of the group experienced prolonged emotional stress (for periods of months) preceding the onset of rheumatoid arthritis. Discussion of their emotional problems caused a fall in skin temperature indicating a change in peripheral circulation. The importance of this mechanism in the development of arthritis could not be evaluated conclusively; its influence appeared to be greater in producing exacerbations of the disease.

Halliday [744] discovered a "definite upsetting event" antecedent to the onset in nine of 20 cases of rheumatoid arthritis, and in seven cases emotional conflicts were thought to have provoked recurrences. The emotional disturbances included shock following acute danger (air raids, assaults and so on), anxiety over finances or the misbehavior of relatives, fear of loss of an object, paranoid resentment concerning superiors, frustration at being jilted and others. The patients were described as having a restriction of feeling and of emotional expression "so characteristic of rheumatoid patients." He pictured patients with rheumatoid arthritis as "a quiet decent lot," with "relative poverty of facial expression," "who habitually hide and repress many aspects of their inner emotional life." Their manner is that of "quiet friendliness," and they do not "fidget or squirm or show obvious nervous movements"; after the onset of their illness the majority have a "cheery" attitude which produces the

effect of "truly touching patience." To Halliday [747] such behavior and moods bespeak self-limitation and restriction of feelings and emotions. He considered that this restriction began in childhood; as children they were shy and retiring; in later life they tended to lead a quiet life, were essentially "home birds" and had obsessional trends, being "markedly orderly, punctual, tidy and overly clean." Of 14 females, eight professed to be either frigid or disinterested in sex; of six males, three were "markedly fixed to their mother or sisters." Halliday [747] summed up the "rheumatoid personality" as a "self-limiting, emotionally inhibited, rather independent (but passively so) type of personality" which not infrequently "is associated with various psychosomatic disorders." During the long period of nightly bombings of Britain, the number of cases at rheumatic clinics increased (Savage [1540]). But most of the rheumatoid arthritics (even the complete cripples) displayed stoicism while the "fibrositics" demonstrated the greatest emotional reaction (Aldred-Brown).

Other Etiologic Factors. Waine, Bauer and Bennett wondered if some causative factor might be circulating in the blood which would be excreted by kidneys and which could be recovered in urine. They injected unprocessed urine from patients with active rheumatoid arthritis, also alcohol and chloroform extracts of urine into 12 rats, but joint lesions did not develop. Freund [600] observed that whereas normal urine digests nucleoprotein from normal joint fluid, urine from rheumatic patients left the added nucleoprotein completely unchanged; the significance was not explained. Changes in water balance were found to affect articular symptoms (Jacobsen and Lichtentritt and Lyons). The adding of ammonium chloride (6 gm. daily) to a fixed diet which thereby produced loss of water resulted in decrease in pain, joint swelling and increase in mobility. The changes were reversed when sodium bicarbonate (6 gm. daily) was added to the diet.

General Conclusions on Etiology. In a word, we are still in the dark as to the cause of rheumatoid arthritis [1094] despite the enormous amount of research carried on during the past years.

Relationship Between Rheumatoid Arthritis and Other Diseases

Rheumatic Fever. The frequent finding of rheumatic carditis at necropsy in cases of rheumatoid arthritis coupled with the not infrequently observed clinical transition of *apparent* rheumatic fever into chronic rheumatoid arthritis has convinced some observers [53, 54, 98] that the two conditions are closely related, if not the same disease with different predominant manifestations. [See data under "Relationship of Rheumatic Fever to Other Diseases" and under "Pathologic Characteristics of Rheumatoid Arthritis: Heart."—Ed.] Collins [359] suggested that rheumatoid arthritis may be a "lente" form of rheumatic fever, and Young and Schwedel stated that there was no fundamental purpose in separating the two diseases. Feiring wrote: "Clinical studies and pathologic findings lend support to the growing conviction that sharp and recognizable differences do not exist between the two diseases. Because the symptomatology overlaps, because the same anatomic elements of the organism are affected, and the same morbid phenomena are expressed, the association appears to be more than simply fortuitous. In fact, the striking and identical features common to both diseases prompt serious consideration of Charcot's premise that, fundamentally, both diseases are different clinical reflections of the same diathesis." Bohan's [170] view was similar. But Hench [814] thought that the two diseases must be carefully distinguished. He maintained that the finding of rheumatic heart lesions in patients with rheumatoid arthritis probably represented "the presence of two coincidental diseases."

[One of us, P.S.H., as an army consultant on rheumatic diseases in the recent war, saw many soldiers whose *presumed* rheumatic fever had slowly progressed into chronic rheumatoid arthritis. But examination in many such cases and of many records failed to reveal a single case in which undoubted rheumatic fever progressed into, or precipitated, undoubted rheumatoid arthritis. In most of the cases the condition was simply acute or subacute febrile rheumatoid arthritis, which in a few weeks became relatively afebrile chronic rheumatoid arthritis. Even in the early "rheumatic fever-like phase" of this acute febrile rheumatoid arthritis much confusion would have been avoided had sufficient attention been paid to the following: the *progressive* (rather than migratory) nature of polyarticular invasion; the general absence of prodromal pharyngitis (although in some cases a confusing pharyngitis occurred after the onset of the arthritis); the slower rises and more moderate elevations of sedimentation rates (rather than the rapid and marked rises characteristic of acute rheumatic fever); the poor effect of salicylates and sometimes the relatively early appearance of roentgenographic changes in joints even in the "rheumatic-fever phase."—Ed.]

Still's Disease. This will be discussed in the section on "Still's Disease and Felty's Syndrome."

Gonorrhea. Like certain other acute infections (influenza, acute respiratory infections) acute genital gonorrhea can precipitate, reactivate or notably aggravate rheumatoid arthritis. Under such circumstances the latter is often mistaken for "gonorrheal arthritis (supposedly) resistant to chemotherapy and fever therapy" (Hench and Boland).

Treatment of Rheumatoid Arthritis

General Remarks. The multiplicity of recommended treatments indicates that no prompt cure is available (Ensign). Most patients do not demand to be cured. They are grateful for small favors and usually are happy if they get some relief (Hench [813]). An optimistic, courageous attitude is required of a physician who does not wish to see some of his patients wander off to patent remedies and quacks. "He must even compromise at times with his intellectual honesty and employ methods of doubtful value to hold the patient to the pursuit of a few simple measures of proved value" (Short and Bauer [1601]).

Management of Foci. No new ideas appeared; the same controversies prevailed.

Some still removed all possible foci,[115] but the majority agreed that only definitely infected foci should be removed,[1487, 1601] and then not to cure the disease but to improve general health.[784, 1370] Focal removal is only one link in the chain of therapy [49] to be recommended "with hope but without promise." Only occasionally does definite improvement follow eradication of an obvious local infection and then usually only in early cases when the onset has been temporally related to a definite infection (such as acute tonsillitis), the site of which can be removed. Well-developed arthritis rarely is benefited (Wetherby [1916]). Key [994] stated that the era of "promiscuous removal of foci" has passed, but Markson warned physicians not to shuttle too enthusiastically to the side of the "belittlers" in a reactionary shift from the older school. Opinions varied as to when foci should be eradicated. Some [344, 434, 994, 1628, 1643] advocated early removal; others advised waiting until the disease quieted down or until the general health improved.[1044, 1604, 1810]

1. Teeth. Devitalized teeth with roentgenographic evidence of periapical abscesses should be extracted.[49, 527, 661, 690, 1809, 1916] The attitude toward devitalized

teeth with no periapical rarefaction was more conservative [527]; such teeth should be checked roentgenographically at intervals,[690] and before extracting them the risk of interfering with nutrition by removing necessary masticating surface must be considered.[1601] Deep pyorrheal pockets were thought to allow as much absorption as abscessed teeth or infected tonsil crypts [527] and should be treated. Shuster claimed that 41 per cent of his 366 patients with early rheumatoid arthritis of less than six months' duration improved after removal of dental foci, but that in only 20 per cent of 215 advanced cases (arthritis of more than two years' duration) was improvement noted.

2. Tonsils. Recurrently inflamed tonsils should be removed.[690, 1601, 1916] Shuster thought that tonsillectomy was of benefit in 50 per cent of 78 early cases and 25 per cent of 84 advanced cases. But Slocumb and his associates [1628] noted definite clinical improvement from tonsillectomy in only 5 per cent of cases in which infected tonsils were the only discoverable focus. [A high percentage of rheumatoid patients seen in private practice have had tonsillectomy long before the onset of their arthritis.—Ed.]

3. Sinuses. Gray warned that articular flare-ups may follow recurrent attacks of sinusitis and that chronic sinusitis should be treated. "Silent sinusitis" must be looked for,[575] but Shuster obtained improvement following sinus surgery in only three of 24 early cases (12 per cent) and in only one (6 per cent) of 18 advanced cases.

4. Gall-bladder, Intestines, Genitourinary System and Female Pelvis. Evidence is distinctly against the importance of these sites as foci of infection according to Short and Bauer.[1601] But the biliary tract [632, 1079, 1907] and the colon [819] were considered as frequent sites of focal infection by some.

Vaccines. "Vaccines have made out a bad case for themselves." [505] The trend now is away from their use, even by some formerly enthusiastic supporters.[605] Such therapy "serves to keep the patient under regular observation and management," [1718] brings him "back to the office repeatedly," [1938] and is useful "for psychotherapeutic purposes." [1643] Ormrod stated that vaccines were harmful because the patient is allowed to "drift into a hopeless and helpless condition" when better measures might have been used.

Proponents of vaccines are diminishing in numbers. Wetherby [1916] continued to obtain results with intravenous use of streptococcus vaccine; of 1,192 patients so treated, clinical improvement was "definite" in 75 per cent. In another series 83 per cent of those receiving vaccine and 40 per cent of those receiving saline solutions were improved (Wetherby [1915]). Vaccines prepared from diphtheroids recovered from lymph nodes of patients with rheumatoid arthritis were used by Cadham; of 500 patients so treated, 37 recovered completely; 377 improved greatly, a total of more than 80 per cent returned to normal occupations. [Such surprising results would be more impressive if confirmed by others.—Ed.] With the use of streptococcus-staphylococcus combined antigen (streptococcus toxin-bacterial suspension combined with staphylococcus toxoid-bacterial suspension) 47 per cent of 34 patients resumed work and 29 per cent more showed improvement.[1875] But Parker's results with Crowe's vaccine were no better than results from injections of normal saline. [Evidently almost any old vaccine works.—Ed.]

Foreign Proteins. Injections of triple typhoid vaccine to produce foreign protein reactions and "general stimulation of metabolism" were recommended for selected cases.[302, 633, 1094, 1177, 1487, 1755] Wetherby [1916] was not impressed with such therapy, and Key [994] stated that in early active cases it often aggravates rather than benefits. Two sudden fatal reactions were recorded (Love and Driscoll; Urbach). At necropsy in both cases [one of rheumatoid arthritis; one

of choroiditis.—Ed.] findings resembled the Sanarelli-Schwartzman phenomenon noted in experimental animals: widespread cutaneous and visceral petechiae; intense congestion of lungs and intestines, and renal, hepatic and adrenal necrosis. Two cases of severe renal irritation (gross hematuria, marked reduction in renal function) after typhoid vaccine therapy were reported (Taylor and Page); both patients had pre-existing renal disease but no arthritis. A patient who had been taking cinchophen had fatal acute yellow atrophy of liver after two intravenous injections of typhoid vaccine; recent cinchophen therapy was therefore considered a contraindication for typhoid vaccine (Yott).

Bee Venom. Only five of 24 patients treated by Hollander were notably improved. Results were considered "very discouraging." [We agree.—Ed.] Banghart was more encouraged; nine of 16 patients were markedly improved, five moderately improved. [Only two failures?—Ed.] Bee venom acts only as an analgesic; comparable results were obtained with injections of magnesium sulfate (12.5 per cent [343]).

Cobra Venom. The use of cobra venom to control pain of rheumatoid arthritis was disappointing to Talkov and Bauer. Only three of 12 patients experienced transient relief; no objective improvement resulted. Acetylsalicylic acid was found to be a better analgesic. But Albee and Maier reported satisfactory relief in 28 of 32 patients.

Diet. Most patients with rheumatoid arthritis lose weight; hence, a high caloric diet complemented with adequate vitamins and minerals is indicated.[46, 567, 606, 784, 1294, 1372, 1487, 1629] Pemberton and Scull [1373] estimated that the diet for afebrile arthritic patients of essentially normal weight at rest in bed should contain a caloric value of about 10 per cent more than the calculated basal energy transformation. One author [1822] claimed that certain patients with "arthritis" were greatly benefited by eliminating food to which they reacted allergically by cutaneous tests.

Vitamins. The daily vitamin requirement of patients with rheumatoid arthritis may actually be above normal (Kuhns [1044]). However, there is no known antirheumatic vitamin, nor has it been shown that any vitamin has a direct relationship to the disease. Vitamin therapy at most is only a "booster" to general health, not a specific remedy for arthritis.

1. Vitamin A. The course of the disease is apparently not altered if a coexisting vitamin A deficiency is corrected.[605, 994]

2. Vitamin B. Supplemental vitamin therapy with the elements of the B complex may improve general health. Because painful neuritis may often be relieved dramatically by thiamine chloride, it was hoped that the pain of rheumatoid arthritis might be relieved also; but massive doses of thiamine were ineffective (Freyberg [605, 606]; Key [994]).

3. Vitamin C. Although ascorbic acid levels in blood plasma are frequently subnormal, the disease was not altered even when "the blood was kept saturated with vitamin C for periods of three months or more" (Key [994]).

4. *Vitamin D.* Although used unenthusiastically since 1935 and previously unheralded, high potency vitamin D therapy has currently become a "popular" treatment for rheumatoid arthritis because of recent "flamboyant advertising" [416] and publicity which "overemphasizes part truths and overlooks the rest of available information." [1629] Vitamin D in large doses may provide subjective improvement (reduction in pain) in some cases of rheumatoid arthritis (Steck). Seven (50 per cent) of 14 patients treated by Slocumb [1626] with daily doses rang-

ing from 52,500 to 386,000 units noted some subjective relief, but few or no objective changes. Freyberg [605, 606] noted some subjective relief in 14 (39 per cent) of 36 patients, objective improvement in only six (17 per cent). Reductions in sedimentation rates of erythrocytes and alterations in the clinical course were rarely noted. Wagner evaluated end results one year after massive vitamin D therapy. Of 32 cases, results were "excellent" in five, good in two, fair in 18, poor in two, and none in five (i.e., notable in only seven cases, 22 per cent).

Many believed this treatment to be of little value.[180, 968, 994, 1718] Boots obtained as good results with plain cod liver oil given as a tonic. But some [542, 1084, 1085] remained enthusiastic. Snyder, Squires and associates [1659, 1660, 1661, 1662, 1806] noted objective improvement more often than others and claimed partial or complete remissions in about 60 per cent of cases.

[De Kruif's [457] enthusiastic article about vitamin D and ertron in "The Readers Digest" entitled "Hope for the victims of arthritis" might better have been called "False hope for the victims of arthritis": so wrote certain commentators.[180, 416] We agree.—Ed.]

Massive vitamin D therapy is not without danger.[595, 1044] Although it takes three to six months after withdrawal for the serum concentration of vitamin D to fall to normal,[1872] toxic symptoms usually subside quickly after administration is stopped. Early signs of toxicity (sweet taste, nausea, vomiting, polyuria, polydipsia, occipital headache) were discussed (Slocumb and Polley [1629]). Severe renal damage from deposition of calcium in renal parenchyma with resultant azotemia, albuminuria and cylindruria may result if these symptoms are ignored; two such cases, one with extensive ectopic calcification about joints, were reported.[432] Toxic reactions were said to be encountered less often with the electrically activated vaporized sterol (Whittier process) than with ultraviolet irradiated ergosterol (Steenbock process [1452, 1662]). Others stated that ertron is also capable of toxicity.[595, 1186] [Severe, even fatal, toxicity has also accompanied the use of "ertron."—Ed.]

5. Vitamin E. In 22 cases rheumatoid arthritis was treated with wheat germ oil (4 to 8 c.c. daily) for six to 18 months.[1732] "Definite improvement" was claimed in 77 per cent. [The "inevitable 75 per cent!"—Ed.]

Endocrines. Results from use of estrogen in a few cases of rheumatoid arthritis (males or females) were satisfactory to some,[1138, 1282, 1732] not to others.[605, 1625]

Transfusions; Hematonics. Repeated blood transfusions may sometimes initiate a remission [784] when marked anemia (values for hemoglobin of less than 10 gm.) will not respond to iron salts.[523, 1629]

Vasodilators: Histamine; Choline and Others. Transient symptomatic relief may follow the introduction of vasodilating drugs, histamine and acetyl-β-methylcholine chloride (mecholyl chloride), into the skin by iontophoresis.[1671] Smith and Freyberg noted some subjective improvement "for a short time" in 79 per cent of 28 patients so treated but on reëxamination only 11 per cent maintained any improvement; few had objective improvement. Such treatment is useful only when small joints are involved,[1120] when local heat cannot be tolerated because of paresthesia [1082] or hot weather [1031] and when hyperemia fails to result from simpler methods.[1487] But "great symptomatic relief" in arthritis (unspecified as to type) was claimed by others.[779, 1448] Repeated lumbar paravertebral blocks with procaine hydrochloride to produce vasodilatation were recommended for persistently painful joints of lower extremities.[1288] Nicotinic acid was given both orally and intravenously in large doses

for its vasodilating effect to 35 patients with rheumatoid arthritis (Kurtz). Intravenous dosage consisted usually of 200 to 400 c.c of a 0.05 per cent solution. Oral dosage consisted of 50 to 200 mg. every 15 minutes for three doses twice daily. Significant subjective improvement was claimed in 15 of 35 cases and marked or moderate objective improvement in 26. [Criteria for improvement, duration of results and follow-up studies were lacking.—Ed.]

Sulfur. Treatment with sulfur has been discontinued in most clinics.[290] Freyberg [606] concluded: (1) no sulfur deficiency or abnormality of sulfur metabolism exists in arthritic patients, and (2) there is no biochemical or metabolic indication for, or benefit from sulfur medication in arthritis.

Sulfonamides. These proved useless in rheumatoid arthritis.[175, 1525]

Penicillin. Because of the effectiveness of penicillin against a variety of infectious agents, especially hemolytic streptococci, many were hopeful that it might prove effective against rheumatoid arthritis. Boland, Headley and Hench gave penicillin daily for 10 to 14 days (daily doses from 120,000 to 320,000 Oxford units and total doses from 1,800,000 to 3,250,000 units) to 10 soldiers with early progressive rheumatoid arthritis: results were negative. Of the 10 patients seven did not improve, one was worse, one showed slight subjective but no objective improvement, and one demonstrated moderate objective and subjective improvement in some, but not all, involved joints. Because of the capricious nature of rheumatoid arthritis the improvement in the two cases was regarded as unrelated to the penicillin. In view of the negative results these authors concluded: "It does not seem unreasonable to assume that rheumatoid arthritis is not caused by any of the bacteria which are already known to be rapidly affected by penicillin." Comroe's results [365] were similar. Six patients given total doses of 1,400,000 to 3,300,000 units (for two to four weeks) received no benefit. Penicillin administered intramuscularly to rheumatoid arthritics was found to penetrate rapidly into joint fluid and to attain levels comparable to those in blood serum.[63] Maximal antibacterial quantities persisted longer in joint fluid than in blood serum, but penicillin did not accumulate in joint fluid.

Bile Salts; Liver Extract. No new data appeared.

Analgesics. Much comfort usually can be obtained from the wise use of analgesics. Salicylates are usually more effective than other drugs.[606, 1070, 1157, 1643, 1968] Patients can go on taking 40 to 60 grains (2.6 to 4 gm.) of acetylsalicylic acid daily without apparent harm.[170, 418] Calcium acetylsalicylate (calsamate) produced less gastric irritation in animals than did acetylsalicylic acid.[1744] Acetophenetidin is sometimes more effective than salicylates [1916]; after review of the literature Cohen [340] concluded that "little or no evidence exists to justify the inclusion of acetophenetidin in the category of dangerous drugs." The dangers of cinchophen were again mentioned.[418]

Demerol, a new synthetic analgesic which approaches the potency of morphine, given parenterally in 100 mg. doses every four hours, usually controlled rheumatic pain of any severity (Batterman). Given orally, "complete relief" was achieved for seven of 14 ambulatory patients with rheumatoid arthritis; about the same results were obtained regardless of whether 50, 75 or 100 mg. doses were given. Ambulatory patients often experienced unpleasant side reactions (dizziness, nausea, vomiting, rarely syncope). Liability to addiction exists although much less so than with opium derivatives. [Because of the liability to addiction we cannot recommend its use for such a chronic disease as rheumatoid arthritis.—Ed.]

Antireticulocytotoxic Serum. The "A.C.B. serum" of Bogomoletz ("antireticulocytotoxic serum," "Russian serum") was used unsuccessfully by Bach.[48]

This serum is produced by immunizing horses with cells of spleen and bone marrow obtained from a human corpse. Presumably antibodies so produced "stimulate" or "block" the reticuloendothelial cells of the recipient. The serum is supposed to "intensify immunity," using "the recipient's tissue as antigens." As a result "the complement in the blood and the opsonic index are increased," and "the sedimentation rate falls if increased, and increases if low." It is said not to act directly on microorganisms but on "the reactivity of the physiological system of the connective tissue," "the condition of which determines the destruction of pathogenic organisms and their toxins." Bogomoletz claimed success in the treatment of "rheumatism," or "acute arthritis" unidentified as to type.[1951] Bach [48] treated 35 patients with rheumatoid arthritis: improvement was noted in only three. Two of the three patients who improved were "tired Lambeth women" admitted to the hospital for a rest, who received the serum at once; two months later both had had relapses. The third patient had "a marked psychogenic factor"; two months after dismissal she was readmitted, this time being relieved by two injections of distilled water. [One of us, R. H. F., has also been disappointed with his results from this serum in rheumatoid arthritis.—Ed.]

Miscellaneous. The night cramps in calf muscles of patients with either rheumatoid or osteoarthritis were relieved by one daily dose of quinine sulfate (3 grains or 0.2 gm.) at bedtime.[680] Chaulmoogra oil still had one advocate.[259] Histaminase was tried "without startling results" (Muether). Crowe [412] injected 1 per cent acid phosphate into 280 swollen painful joints and claimed "lasting relief" in three fifths and "temporary relief" in all the rest except one. Good results in arthritis were claimed with "systemic disinfection" using "thyroid substance and potassium permanganate." [1307] Nott stated "this treatment has been before the medical profession for seventeen and a half years without one word being published against it." [Shall we be the first to do so?—Ed.] "Eaton's formulae," concoctions containing cinchophen and neocinchophen in combination with methenamine, sodium cacodylate and so forth, as well as "imperial draught" were described.[493]

Spinal "Pumping." Rheumatoid arthritis is a neurodystrophy according to Speransky (1935). For curious reasons (discussed under "Treatment of Rheumatic Fever") he applied spinal pumping to 15 patients with "chronic arthritis": four recovered; nine improved; two did not. The Gillmans [653] used spinal pumping in connection with salicylates given orally: 60 patients with "various types of rheumatoid arthritis" were treated. "Improvement" was often noted within 24 to 48 hours and was sometimes "striking" within four hours of the pumping. Reportedly 80 per cent of the patients with subacute disease (numbers not stated) were "discharged as cured at the end of three days." [Most difficult to believe.—Ed.] Relapses were "not uncommon."

[The Gillmans [654] recently made a second report on results in 70 cases of various rheumatic diseases including 22 of "chronic arthritis." As in the previous report the terminology used was vague, claims made seemed extravagant; the rationale unacceptable. The procedure may not be without danger: one death occurred.—Ed.]

Neostigmine (Prostigmine). This was used by Trommer and Cohen in 19 cases of rheumatoid arthritis with "a maximum of deformity but a minimum of active joint involvement." A test dose of 0.5 mg. of neostigmine methylsulfate and 0.6 mg. of atropine sulfate was usually first given, then daily maintenance oral doses of neostigmine bromide (7.5 to 45 mg.) with tincture of belladonna (0.6 to 1.2 c.c.). Marked relaxation of muscle spasm, increased motion and relief of pain from muscle spasm (but not relief of articular pain) were claimed

in 16 of 19 cases. When the drug was given subcutaneously, beneficial effects were said to occur within 15 minutes and to persist for several days (Cohen [341]). But prostigmine produced a "depressing effect" on the atrophying muscles of animals with experimental chemical arthritis.[618]

[The early favorable results from use of neostigmine for neuromuscular dysfunction were editorially considered "insufficient for critical evaluation."[507] However, neostigmine was De Kruif's[458] arthritis remedy for 1946. His misleading overoptimism also was criticized in an editorial.[508] More recently Cohen, Trommer and Goldman reported that neostigmine is inferior to physostigmine. At the 1946 meeting of the American Rheumatism Association several speakers (Pemberton, Lewin, A. S. Gordon, Traeger, Freyberg, C. J. Smyth) expressed disappointment with this type of treatment.—Ed.]

Chrysotherapy. Gold is still extensively used after 20 years of trial and error. The exact value of gold salts in the treatment of rheumatoid arthritis remains uncertain but rheumatologists of experience, with few exceptions, report results therefrom better than those obtained with any other single remedy.

1. Indications. Because of the toxicity of gold salts American physicians until recently have restricted their use to cases of rheumatoid arthritis not amenable to more conservative measures. This practice is still adhered to by some,[366, 1513, 1569, 1629, 1664, 1916] but others have recommended early use of gold.[307, 739, 784, 1648, 1713, 1946] Chances for complete remissions appear to be better if chrysotherapy is used early (Cecil [304]), and some believed that to delay until other forms of treatment have failed is an unjustifiable waste of time (Cohen, Goldman and Dubbs) which permits unnecessary discomfort and the development of irreparable joint damage.[1477] Others urged that chrysotherapy be delayed for at least three to six months after the onset of rheumatoid arthritis or until the likelihood of spontaneous remissions seemed remote.[1590, 1664, 1713] Extreme views were expressed by Robinson [1478] who stated that gold should be used in any case of rheumatoid arthritis in which the sedimentation rate is elevated, and by Key [994] who stated that "it should be employed in every case." Gold salts should not be used in any rheumatic disease other than rheumatoid arthritis, with the possible exception of psoriatic arthritis.[306, 686, 1064]

2. Contraindications. Contraindications listed were severe diabetes mellitus, nephritis, ulcerative colitis, hepatic insufficiency, blood dyscrasias and hemorrhagic tendencies.[1648, 1713, 1715, 1946] Allergy,[1044] pregnancy [686] and history of exfoliative dermatitis [366] were also mentioned, but hypertension was not considered a contraindication.[1713] Hartung [784] warned against chrysotherapy in the presence of associated acute rheumatic fever with or without carditis, or of disseminated lupus erythematosus (in contradistinction to the discoid type in which gold salts may be employed).

3. Preparations. Several preparations of gold salt are now marketed. Those usually used in the United States are listed in table 3.[607, 784, 1064]

Colloidal gold preparations, including the sulfide, being of little therapeutic value [607] have generally been discarded (Freyberg, Block and Levey [610]).

4. Dosage and Methods of Administration. Most preparations are given intramuscularly; gold sodium thiosulfate may be given intravenously. Gold is the active principle and since the gold content differs in various salts, dosage must be figured in equivalent doses of gold.[607] A favored schedule of treatment with myochrysine (50 per cent gold) has been to inject increasing amounts of the salt, from 10 mg. to 100 mg. weekly, until a total of 1 to 1.5 gm. has been given. Gold thioglucose (solganal-B oleosum) also contains 50 per cent gold, but is absorbed less readily and to have an equal amount of gold retained about 125 per cent of the dose for myochrysine is re-

TABLE III

Gold Salts Available in the United States

Chemical Name	Proprietary Name	Solubility in Water	Physical State	Gold Content, Per cent
Gold sodium thiosulfate	Sanochrysine	+	Aqueous solution	37
Gold sodium thiomalate	Myochrysine	+	Aqueous solution	50
Gold calcium thiomalate	Calcium aurothiomalate	−	Oil suspension	50
Gold thioglucose	Solganal-B oleosum	+	Oil suspension	50
Gold thioglycolanilide	Lauron	—	Oil suspension	54

quired (Freyberg [606]). Gold thiosulfate is only 37 per cent gold, hence proportionately larger doses are needed. Because fewer toxic reactions result from smaller weekly doses, most authorities do not give more than 50 mg. of gold salt (about 25 mg. of gold) per week (e.g., myochrysine and solganal-B oleosum).[739, 740, 784, 1754, 1916] Freyberg [606] found that weekly doses of 50 mg. of gold salts were as effective as doses of 100 mg., but that weekly doses of 25 mg. gave inferior results. Others (Buttorff [271]; Rawls and associates [1438]) claimed equally good results with doses not exceeding 25 mg. (solganal-B oleosum) per week. Usual practice has been to give one, two or more courses of gold salts (total 1,000 to 2,000 mg. each course) with rest-periods of two to six months between courses. The frequency of relapses during rest-intervals prompted Freyberg and his colleagues,[613] Boots and Ragan, and others to give a single course followed by small maintenance doses every week or so for several months longer. [The plan of continuing maintenance doses has now been widely adopted. —Ed.] Much larger doses of a newer preparation, gold thioglycolanilide (lauron), claimed to be substantially less toxic, were recommended.[1479, 1713] Robinson [1479] advocated initial doses of 25 mg.; then he gradually increased the weekly dose to as high as 300 mg. Total doses as great as 3,750 mg. in one course were given. [Two of us, D.C.C. and R.H.F., have noted severe skin reactions to lauron. Those who have studied the metabolism of gold salts find it difficult to understand how any "insoluble" gold compound such as gold thioglycolanilide (lauron) can be depended on to give consistent results. With such salts speed and amount of absorption and elimination vary widely, and when they are not tolerated prolonged toxic reactions may occur. Even if they were nontoxic, the use of such large doses is difficult to rationalize. Before they are considered superior to the aqueous soluble preparations, such insoluble compounds must provide greater benefits than have yet been reported.—Ed.]

5. Mode of Action. Our knowledge of the metabolism of gold salts is much greater than it was five years ago, still "it is not known where, how or why gold salt therapy works" (Freyberg [607]). Hartung found no evidence that gold salts stimulate the reticuloendothelial system or increase blood agglutinins. Gold sodium thiomalate (myochrysine) was an effective chemotherapeutic agent in the prevention of arthritis produced in rats by hemolytic streptococci, but the preventive dose was close to the lethal dose, and gold was not as effective prophylactically as either sulfanilamide or sulfathiazole, nor did it cure the disease once it was established.[1512] Gold sodium thiomalate is bactericidal in vitro against hemolytic streptococci, type green, in dilutions through 0.000001 per cent and bacteriostatic in higher dilutions.[785] Other common organisms (*Staphylococcus albus, Staphylococcus aureus,* nonhemolytic streptococci, pneumococci, types III and VI) are somewhat similarly affected. In vitro bacteriostasis was roughly proportional to the concentration of gold salt. The bacteriostatic

powers of the patient's serum are markedly increased [785] against hemolytic streptococci, type green, after administration of gold sodium thiomalate, but agglutination titers for this organism are not increased. But since the cause of the disease or the offending organism (if any) has not been demonstrated, it cannot be assumed that clinical results from gold are due to its bacteriostatic effect.[1629]

Sabin and Warren demonstrated that on the pleuropneumonia-like arthritis of mice gold compounds whether inorganic or organic, soluble or insoluble, were capable of exerting a curative effect. But colloidal gold had no therapeutic value. The earlier the arthritis in mice was treated, the more rapid and complete was the response. When treatment was delayed for as long as four weeks (coinciding with the stage of cartilage destruction) the involvement in some joints was irreparable. When the total dose was administered in a week, better results were obtained than when smaller doses were given for a longer period. The experimental arthritis disappeared completely in 96 per cent of 171 mice treated with adequate doses at the proper time.

When glutathione, cysteine or thioglycolic acid is given in aqueous solution with gold salts, their SH group is blockaded, and they do not give the characteristic reaction with sodium nitroprusside, the usual reagent for the SH radical.[1098] Libenson proposed: "Since glutathione and cystein are present in most of the organic tissues, it can be assumed that the gold compounds, either ionic without sulfur or complex gold-sulfur compounds, given parenterally combine with the SH radicals contained in the cells and exert their therapeutic action later as gold-glutathione or gold-cystein complex compounds." But Preston, Block and Freyberg demonstrated in arthritis of mice that the effectiveness of gold compounds is not dependent on a sulfhydryl linkage. Both gold sodium thiomalate (containing sulfur in sulfhydryl linkage) and gold sodium succinimide (containing no sulfur) were effective in curing experimental arthritis. Sodium thiomalate and the disulfide form of sodium thiomalate (neither containing gold) were ineffective; thus it is the gold rather than the sulfur in the gold salts which is the effective element (Sabin).

Block, Buchanan and Freyberg [156, 157] studied the absorption, distribution and excretion of various compounds of gold in rats. Absorption, after intramuscular administration, was related to the physical properties: colloidal preparations (colloidal gold, colloidal gold sulfide) were poorly absorbed as compared to crystalline salts (gold sodium thiosulfate, gold sodium thiomalate, gold sodium succinimide). Following injections, gold was found in kidneys and liver in larger amounts than in other organs. When crystalline salts were injected, gold was found in greater amounts in kidneys, whereas with colloidal preparations gold was more abundant in the liver. The urine was the chief route of excretion of crystalline preparations; the feces, the chief route for colloidal gold. When intramuscular injections of soluble crystalline salts (myochrysine, solganal-B oleosum and gold sodium thiosulfate) were given in increasing weekly amounts, a steplike increase in plasma gold concentration resulted. When weekly doses were kept constant (50 mg. of gold, 100 mg. of gold salts) the concentration in plasma remained relatively constant, usually between 0.4 and 0.8 mg. per 100 c.c. During the period of administration much gold was retained: when weekly injections of 50 mg. of gold (100 mg. of the salt) were given, the average daily excretion of gold was only 1 mg., or slightly more (7 to 10 mg. weekly). Hence, during treatment with crystalline salts about 80 per cent of injected gold remained in the body. After a course of treatment, gold was found in plasma and urine for six to 12 months.[786] After injections of insoluble colloidal gold sulfide, which is therapeutically ineffective, little or no gold was found in plasma, small amounts in feces, and none or only traces in urine; the colloidal particles were phagocytized in large amounts by reticuloendothelium, especially in liver and spleen.[613, 1524]

In vitro studies of oxygen consumption by hepatic and renal tissues as influenced by various gold-containing compounds revealed that the inorganic ionizable compounds

(gold chloride, gold sodium thiosulfate, colloidal gold sulfide) inhibited oxygen consumption, while the organic nonionizable compounds (gold sodium succinimide, gold sodium thiomalate, gold thioglucose) did not.[158] Plasma lipids in cases of active rheumatoid arthritis deviated little or not at all from normal before, during and after chrysotherapy (Bayles and Ridell). [These excellent, important studies on the metabolism of gold by Freyberg, Hartung, Sabin and their colleagues have done much to make chrysotherapy more rational and safe.—Ed.]

6. Results from Chrysotherapy. Bayles and Hall devised a "yardstick" to evaluate results of therapy in rheumatoid arthritis, particularly chrysotherapy. The following criteria were used: functional activity, activity of disease, degree of deformity, sedimentation rate, hemoglobin value, and body weight. [If some workers would use these or similar criteria, they would refrain from publishing vague, uncontrolled and unconfirmable results.—Ed.]

In 100 cases in which follow-up observations for periods of six months to two years were available, the following results of treatment with myochrysine were reported by Dawson, Boots and Tyson: complete arrest in 22, marked improvement in 29, "moderate but very real improvement" in 25, slight improvement in 10, no improvement in 14. Relapses occurred in 12 per cent of cases strikingly improved but the original degree of activity was resumed in "very few." Logefeil and Hoffman reported complete arrest or marked improvement in 65 per cent of 74 patients treated with a single course of gold thiosulfate intravenously (50 mg. twice weekly; total dose of 1,000 mg.). The relapse rate was 15.4 per cent. Treating 250 patients with solganal-B oleosum (graded doses from 10 to 100 mg. and total dose of 1,200 mg.) Gardner noted that 70 to 80 per cent were improved and that 50 per cent of those recently affected and 30 per cent of those affected more than two years were cured. [The number "cured" was not stated. This report seems unduly optimistic.—Ed.] Smyth and Freyberg [164a] found myochrysine and gold sodium thiosulfate to be equally effective; 66 per cent of 53 patients treated with the former and 64 per cent of 11 patients treated with the latter showed moderate or marked improvement or arrest of the disease. Only 25 per cent of 12 patients given colloidal gold sulfide were notably improved.

Cecil, Kammerer and De Prume treated 235 patients: 207 with myochrysine, 40 with solganal-B oleosum, and three with gold sodium thiosulfate. [This totals 250 since some patients received more than one salt.—Ed.] Results were complete remission in 31 per cent, great improvement in 35 per cent, moderate improvement in 20 per cent, no improvement in 14 per cent. Best results were obtained in early cases: in 78 per cent of early cases and 62 per cent of late cases remissions or great improvement occurred. Thirty-four per cent of the patients with remissions and 50 per cent of those "greatly improved" had relapses in from six months to five years; about 50 per cent of the relapses occurred within one year. In only half of those in whom relapses occurred did the disease become inactive again with a second course. In another series 60 per cent of 101 patients treated (91 with myochrysine; 10 with solganal-B oleosum) showed moderate or marked improvement (Price and Leichtentritt). Results depended on the severity of the disease; significant improvement was obtained in 93 per cent of cases of mild disease, 80 per cent of moderate, and 40 per cent of the severe. Graham and Fletcher reported results in 100 cases in which myochrysine was given in doses of 10 to 100 mg. per week (total of 1.06 gm.). Complete remissions were obtained in 16 per cent, marked improvement in 51, some improvement in 20 and

no improvement in 13 per cent. Best results were obtained early in the course and in younger persons. In 54 per cent of 264 cases in which Hartung [784] used myochrysine, remissions were observed but subsequent relapses occurred in 21 per cent; this left 33 per cent in which complete arrest was maintained after one year.

"Improvement of a sort" was obtained in 87 per cent of 122 patients treated by Cohen and Dubbs with solganal-B oleosum (1.24 gm. per course): 35 per cent showed only subjective improvement; 17 per cent were "much improved"; 36 per cent were "very much improved"; 9 per cent showed no change; 4 per cent were worse. [This totals 101 per cent.—Ed.] Summarizing later the results of 417 courses of treatment given 259 patients Cohen, Goldman and Dubbs [344] reported "very marked improvement" in 48 per cent, "marked improvement" in 18 per cent. Rawls and his associates,[1438] using small doses of solganal-B oleosum (25 mg. per week), obtained results which compared favorably to those obtained with larger doses. Definite courses were not given; if improvement occurred, gold salts were used indefinitely, or for at least 12 months. Such a schedule reduced the incidence of relapses. For patients who failed to respond adequately to 25 mg. weekly, the dosage was increased to 35 or 50 mg., but never to more than 50 mg. In 53 of 100 cases the arthritis was markedly improved or inactivated; in 21 definitely improved; in 26 improved slightly or not at all.

Fraser [591] treated 57 patients with myochrysine (one or two courses of 1 gm. each) and 46 controls with injections of a therapeutically inert "control substance." Clinical signs of notable improvement occurred in 63 per cent of those who received gold salts, in only 21 per cent of the controls. Degrees of improvement in the two groups were in greater contrast: "great improvement" occurred in 42 per cent of those given gold and in only 8 per cent of the controls. Moreover, in 18 per cent of the former and 55 per cent of the controls the disease remained stationary or became worse. [This study deserves special attention as it and that of Ellman, Lawrence and Thorold (1940) constitute the only two reports on gold therapy which mention controls so far as we know.—Ed.] Robinson [1478] treated 200 patients with myochrysine. "Approximately 25 per cent" were "cured," about 25 per cent were greatly improved, about 25 per cent showed some improvement, and the remaining 25 per cent were not helped.

Short's [1598] results with chrysotherapy contrasted to those of others; only six (19 per cent) of 31 patients showed noteworthy subjective and objective improvement, and three of these later had relapses. Stengel treated 30 patients with gold thioglycolanilide (lauron); in three cases (10 per cent) the disease was arrested; in 17 (57 per cent) markedly improved, in seven (23 per cent) moderately improved, and in three (10 per cent) worse. Using gold calcium thiomalate (50 mg. weekly for 12 injections; total dose 600 mg.) Ray [1440] found that 50 per cent of 50 patients showed definite improvement; 25 per cent were somewhat improved; and 25 per cent noted no change.

7. Toxic Reactions. The usual toxic reactions (dermatitis, mild rash to exfoliative type, ulcerative stomatitis, ulcerative colitis, hepatitis, thrombocytopenic purpura, agranulocytosis, aplastic anemia, bronchitis, and so forth) were encountered.[342, 591, 628, 739, 1122, 1499, 1569, 1629, 1791, 1946] Usually they did not occur until after several hundred milligrams of the drug had been given [606] but they may occur after small initial doses (20 to 30 mg.), during a second or third series, or even weeks after

treatment is completed.[1663] All but one worker encountered toxic reactions; Stengel, using lauron reportedly had none in 30 cases. Ten writers reported the percentages of reactions in their cases; they averaged 37 per cent, ranging from 8 to 61. Most reactions were minor and disappeared promptly on discontinuance of the treatment. Serious reactions occurred in not more than 5 to 10 per cent of cases.[450] Short,[1598] reviewing earlier literature, found the mortality rate in a combined series of 1,800 cases to be one in 200 cases (0.5 per cent), a rate 10 times higher than for neoarsphenamine in the treatment of syphilis. But Hartung noted only one death in "well over 1,000 cases." Cecil, Kammerer and De Prume had one death (ulcerative enteritis) in 245 cases; Dawson, Boots and Tyson had one from thrombocytopenic purpura in 101 cases. A death from multiple cerebral hemorrhages after chrysotherapy was reported[1665]: 0.10 gm. of brain tissue contained 0.035 mg. of gold, "a very appreciable figure." In two cases latent syphilis was thought to have been reactivated by chrysotherapy.[1340] [The mortality rate in all reported cases has been about one in 250 cases (0.4 per cent), but the incidence of serious or fatal reactions is expected to be lowered materially by the use of BAL.—Ed.]

Little is known regarding the nature of the reactions; they probably reflect something other than simple intoxication from a heavy metal.[1499] In the blood gold is combined intimately with serum protein; perhaps gold proteinate may be allergenic in persons in whom toxic reactions develop.[612] Libenson suggested that toxicity might result from the action of gold on the organic sulfhydryl compounds of the body; by blockading the SH groups of glutathione, cysteine and other sulfhydryl compounds, the normal oxygen-reduction process in cells may be prevented.

8. Prevention and Treatment of Toxic Reactions. No constant indicator signals the approach of a toxic reaction (Rosenberg). Skin tests are of no help (Lintz). A drop in the platelet count to less than 75,000 per cubic millimeter, a fall in the leukocyte count to less than 4,000, eosinophilia, albuminuria, microscopic hematuria and pruritus have all been designated as danger signs. [But they are not constantly reliable.—Ed.] To minimize the frequency of reactions certain precautions should be taken[784]; before each injection ascertain whether a rash or purpuric spots, stomatitis, albuminuria or microscopic hematuria is present; every two weeks obtain leukocyte and differential counts and hemoglobin determination; for "susceptibles" obtain Addis and platelet counts. Gold should not be given by a physician unless he is familiar with the bad as well as the good results (Slocumb and Polley[1629]). Severity and frequency of reactions are reduced when the smaller weekly doses of gold salts are used.[271, 1438] Freyberg[606] noted the following incidences of toxic reactions in relation to dosage: 100 mg. of gold salt per week, 41 per cent; 50 mg. per week, 30 per cent; 25 mg. per week, 18 per cent.

Tarsy[1774] administered "detoxicants" (glycine, cystine, glucuronic and ascorbic acids and choline) to patients under chrysotherapy, but they failed to prevent toxic reactions. Neither vitamin B complex nor cevitamic acid exerted any preventive influence (Cohen[344]).

Apparently there is no means of altering the metabolism of gold to lessen toxic reactions once they occur. "Anyone using the drug is at its mercy" (Freyberg[606]). Minor reactions were treated with nicotinic acid and cevitamic acid with questionable efficacy. For exfoliative dermatitis sodium thiosulfate and calcium salts were recommended (Lintz).

[Until recently these remarks were true. But current results with the use of BAL (British Anti-Lewisite) lead us to hope that an effective method for controlling

at least some of the serious toxic reactions is at hand.[345, 1116, 1426] Nine patients who had exfoliative dermatitis of less than two months' duration, one who had severe thrombocytopenic purpura and one who had granulocytopenia responded rapidly to intramuscular injections of BAL. One patient whose dermatitis had been present for three months was not relieved. Penicillin is also a potent weapon against granulocytopenia which may result from chrysotherapy.[175] These results are indeed promising but should not encourage physicians to lower their guards unduly or prematurely against the hazards of chrysotherapy.—Ed.]

9. Newer Gold Preparations. Determined to find an effective, yet relatively nontoxic preparation, physicians have continued to try new salts of gold. Whereas, the therapeutic value of soluble gold salts seems to depend chiefly on the concentration of gold, the toxicity apparently is influenced by the nature of the attached radical and by the solubility or relative insolubility of the compound. An insoluble preparation, calcium aurothiomalate, was found by Sabin to be relatively nontoxic (as measured by lethal effect on mice) and as therapeutically effective in arthritis of mice as sodium aurothiomalate (myochrysine). In humans this preparation apparently was devoid of organ-toxicity but reactions in skin and mucous membrane did occur. [Some were severe.—Ed.] Calcium aurothiomalate was found by Ray [1440] to be about as effective as soluble preparations. More recently gold thioglycolanilide (lauron) has been marketed. According to some (Robinson [1479]; Stengel) this compound is "superior to other gold compounds in its beneficial effects" and "far less toxic." Although larger individual doses of the compound were used (up to 311 mg.), three of 55 patients treated by Robinson [1478] had "a slight rash," one an abscess of the buttock and several a "mild sore mouth"; no other toxicity was noted. [Some of us have had considerable clinical experience with this compound and have noted mild albuminuria and severe prolonged dermatitis. In our opinion it possesses no special therapeutic advantage and all the potential disadvantages of other commercial gold preparations.—Ed.]

10. Conclusions on Chrysotherapy. Chrysotherapy offers greater promise than any other form of therapy according to Dawson, Boots and Tyson, but they warned of its dangers. When carefully given its good effects far outweigh the risk involved (Hartung [784]). Wetherby [1916] considered the results from gold therapy encouraging, "although like vaccine it has only occasionally been followed by clinical cure when used in patients with a well-established arthritic process." In the experience of Smyth and Freyberg [1648] gold therapy was "valuable in many cases" but "not uniformly beneficial" and "its potential toxicity is a definite objection to general use." Several [434, 591, 686, 739, 740, 1478, 1713] cautioned against relying on gold alone; chrysotherapy may be an important adjuvant but the patient should also be given the benefit of the general measures included in a conservative regimen. Cutts summarized the case for gold salts as follows: "Certainly their use is attended with real danger and even the best results are far from spectacular. In short, in the present stage of our knowledge there is no royal way to recovery from rheumatoid arthritis." Contrasting views were held on the one hand by Key [994] who stated that chrysotherapy should be employed in "every case" of rheumatoid arthritis, and on the other hand by Short [1598] who concluded that "it carries a danger of toxicity too great for any but an indispensable drug."

Bismuth. In an attempt to find other metals as effective but less toxic than gold a few workers have employed bismuth. Various degrees of improvement were claimed for 60 per cent of patients with "arthritis" given sodium bismuth tartrate (Hall [741]), but Douthwaite was not impressed with such treatment for

rheumatoid arthritis. Tarsy [1773] tried colloidal bismuth and colloidal platinum, metals with atomic weights approximately that of gold; results were essentially negative.

Fever Therapy. The recent trend has been to deprecate artificial fever therapy.[554, 1656] Of 74 patients treated thereby (104° to 105° F. rectally for six sessions of three hours each; Kettering hypertherm), 44 per cent showed immediate improvement, but in only 18 per cent was it sustained after six months (Fetter and Schnabel). Osborne, Markson, Driscoll and Merriman submitted 27 patients to six or eight sessions of hyperpyrexia at 104° F. for four hours, induced by electromagnet. Improvement was marked in 22 per cent, moderate in 22 per cent, slight or none in 56 per cent; follow-up results were not reported. Concentrations of ascorbic acid in plasma were not changed notably by induced hyperpyrexia. Typhoid vaccine reactions were as effective as prolonged artificial fever.[633] Prolonged fever induced with typhoid vaccine given by intravenous drip was again described.[1021]

Roentgen Therapy. Although results from roentgen therapy in rheumatoid spondylitis were encouraging, those in peripheral rheumatoid arthritis were so discouraging that Smyth, Freyberg and Peck abandoned such treatment. But others [183, 990, 1754] reported "excellent results" when local irradiation (600 to 900 r) was applied to severely involved joints resistant to other measures; swelling often diminished; pain and soreness subsided; muscle spasm relaxed and mobility increased (if ankylosis was not present). Extravagant claims were made by Watt, who stated that "clinical cure" could be expected in 90 per cent of early cases, "arrest of further progress" in 80 per cent of moderately advanced cases, and "decrease of pain, more freedom of motion and arrest of further progress" in 70 per cent of advanced cases. Effusions of knees from "nonspecific synovial lesions" [rheumatoid arthritis?—Ed.] were eliminated from eight of nine joints treated by Horwitz and Dillman, but "asymptomatic synovial thickening" persisted in three joints. The same workers applied large doses of roentgen-rays (total doses as great as 8,000 r) to normal joints of dogs and on histopathologic examination found no evidence of articular damage resulting therefrom (dogs killed at varying intervals up to three and one-half months after exposure).

Radon. Local applications of radon ointment were considered useful,[1134] but Kaplan [946] condemned this remedy because it had little penetrating power, for radon is rapidly dissipated in air. Radon ointment proved "absolutely ineffective and useless for arthritic conditions"; to assume "it can influence the underlying joints or bones is entirely erroneous" (Kaplan [946]).

Rest and Motion. The importance of general physical and mental rest and rest for involved joints was stressed.[46, 567, 1082, 1671] Simple rest is hard to enforce especially when patients begin to "feel a little better," but the physician must be firm to prevent reactivation and fatigue at any cost (Markson). Pemberton [1364, 1365, 1371] stated that rest as a form of therapy is neglected by physicians; a survey showed that less than 11 per cent prescribed it. Most writers agreed that complete rest in bed was indicated only in severe, acute or febrile cases [606, 739, 784] and during flare-ups with local heat and severe pain.[860] But Stevens [1718] took an extreme view and advised complete rest in bed "until all clinical and laboratory signs of activity have subsided, even in long-standing chronic cases." [Such advice is unrealistic and may be dangerous unless exercises and special care are used to prevent deformities.—Ed.] In chronic cases the minimal amount of rest should be 10 hours at night and two periods of one hour each during the day.[418, 1487] During such periods affected joints should be placed in the best position to insure maximal function should deformity develop.[1629] Opti-

mal positions were described.[1671] Daily systematic passive and active exercises to prevent joint stiffness and muscle atrophy are of utmost importance [606, 926]; during the more active stages these should be gentle and nonweight bearing.

Physical Therapy. Many general articles appeared.[97, 230, 295, 400, 411, 627, 801, 859, 880, 927, 1029, 1030, 1036, 1204, 1245, 1250, 1299, 1367, 1389, 1390, 1409, 1554, 1882, 1923, 1948, 1949] The value of home physical therapy by simple means (radiant heat, contrast baths and douches, wet packs, paraffin baths, hot tub baths, and others) was stressed.[606, 1332]

Proper use of heat, massage, passive and active exercises can be taught to the patient or his family; home physical therapy is something which can be used every day of the year.[395, 926, 1487, 1650] An electric pad or cheap heat lamp used consistently is of more value than elaborate machinery which is only occasionally available.[1157] Treusch and Krusen made a follow-up study on 218 patients with arthritis for whom home physical therapy was prescribed. Of these 93 per cent carried out the prescribed treatments at home; 65 per cent continued the treatments for three months or longer. Two thirds (66 per cent) appeared to be benefited thereby. Treatments were more likely to be carried out and results were better when more than one period of instruction had been given; rheumatoid arthritics constituted the most diligent group. Copeman [376] improvised methods of applying physical therapy in a military field hospital: sweat baths with a makeshift cabinet covered with blankets and the steam provided by boiling water in a five gallon can; a hot air bath made with two cradles covered with blankets and connected by a length of piping to a primus stove; radiant heat lamp improvised from petrol cans.

The physiologic effects of local heat differ but little whether they are conductive (electric pad, hot packs, hot water bottle), convective (infra-red lamps, bakers) or conversive (diathermy), except that the first produces the least penetration and the last the greatest.[1036, 1388] Light massage over muscles with the stroke directed to help the return flow of venous blood aids in circulation and relaxation,[1629] but joints themselves should not be rubbed [1643]; "there is no place in inflamed tissues for the use of ploughing, pounding and punching methods which only increase inflammation" (Ober [1310]). Massage does not increase muscular strength; this can be brought about only by active exercises.[1388] In general, exercises of joints should be begun as soon as any degree of painless motion is possible.[522] For an acutely swollen painful joint exercises should be delayed, but to wait too long favors development of permanent disability.[1671] Exercises must be supervised and graduated [1487]; "purposeless wiggling of joints" should be condemned (Slocumb and Polley [1629]). Exercises should not be done too enthusiastically, and if increased pain persists for more than two hours thereafter, the exercise has been too vigorous.[593, 1487] Salicylates beforehand may aid in accomplishing joint movement. The value of underwater exercises, especially in a Hubbard tank, was pointed out.[860, 1082, 1655] Solomon [1671] outlined a useful set of simple joint exercises and a simple exerciser for knees was described (Newman). Electrical muscle stimulation is a "lazy man's way of exercising" (Osgood) and has little place in the treatment of rheumatoid arthritis, but active muscle training, such as muscle-setting and resistant exercises, is of great importance and should be begun early.[367]

Occupational Therapy. Discussions on the aims and importance of occupational therapy appeared.[81, 771, 800, 988, 1099, 1140, 1329, 1343, 1489, 1529, 1841]

Occupational therapy is concerned mainly with the restoration of joint motion and muscle strength; it provides the patient with something constructive or useful to do, thereby ridding him of a feeling of helplessness and dependency.[160, 264] Movements involving extension rather than flexion should be encouraged.[860] Hurt gave the following principles for muscle building: for a poor muscle, exercise with gravity

eliminated; for a fair muscle, exercise against gravity or its equivalent; for a good muscle, exercise against gravity and graded resistance. Various measures and equipments were described.[264, 396]

Spa Therapy. Several general articles described spas and their facilities.[1005, 1570] The chief advantage of a spa is that it removes the patient from his everyday work and worry and places him in an environment of rest and recreation.[1032] To stay at one of the "watering places" twice a year may be of some help,[1643] but patients in active stages of rheumatoid arthritis do better at home or in a hospital.[359] The Medical Advisory Committee for Chronic Rheumatic Diseases (Scotland) [1215] concluded that mineral waters possess no antirheumatic properties and that the therapeutic effects of spas are due to extraneous and accessory factors, not to the inherent qualities of the waters. According to Markson, "the health resorts have lost most of their reputation due to shady methods, absurd claims to healing virtue and the frequent presence of shady medical direction."

Climate. Many patients with rheumatoid arthritis receive symptomatic benefit from a constant, warm dry climate,[1288] but in the experience of Cecil [305] those who respond most conspicuously relapse sooner or later when they return to their usual climatic environment. Although some doubt the importance of climatic influence, the fact remains that rheumatoid arthritis is rare in the tropics and diminishes in incidence toward the south [1157]; if the ugly northern winters can be avoided so much the better, but it is hardly practical in most cases to urge a patient to disrupt his livelihood to move to a warmer climate. According to Hill and Holbrook a warm, dry climate is helpful and for some patients "specific." Patients who had failed to improve on a conservative regimen improved on the same program after moving to southern Arizona. Seven patients with severe rheumatoid arthritis were kept by Edstrom [509, 510] in "tropic chambers" with the air in the room at a constant temperature of 32° C. and a humidity of 35 to 40 per cent, a relatively warm but dry tropical atmosphere. Four patients became free of symptoms and capable of working; three (including one with Still's disease) improved temporarily but had relapses when treatment was stopped. Improvement was attributed to bettered peripheral circulation and increased relative oxygen saturation of venous blood.

Psychotherapy. Psychotherapy often serves as an important adjunct to more realistic therapy. To prevent attitudes of dependency, helplessness, frustration and self-pity the patient needs: (1) restoration of self-reliance; (2) development of a reasonably optimistic view as to prognosis; (3) avoidance of quackery; (4) persistence in carrying out standard methods of treatment; (5) financial help in some cases; and (6) occupational rehabilitation (Hench [813]). Swaim [1751, 1752] added to these a "regime of spiritual training." In his experience anxiety and resentment are the two most constant emotional reactions of arthritic patients, which suggest that maladjusted human relationships are a fundamental problem. Sometimes the patient, often the whole family, needs a change of heart, a new spirit of cooperation and interest.

The natural clinical course of the disease often fluctuates with the mental state. Halliday [747] repeatedly noted the ameliorating influence of a new interest added to a cramping life situation, "giving the patient something to live for." Functional symptoms may be superimposed on those from the arthritis; pain may be disproportionate to the activity and extent of the disease (Short and Bauer [1601]). The physician should

discover and eliminate those fears and conflicts responsible for a low threshold of sensitivity. Perhaps the benefits from most forms of current treatment result from psychic effects (Davis [448]). In one series significant improvement resulted in 40 per cent of patients given injections of sterile saline (Wetherby [1915]). According to Markson [1157] "anything short of that which smacks of down and out quackery" may be instituted for discouraged patients rather than allow them to discontinue treatment entirely. [We would add: provided that (1) it doesn't cost the patient too much and (2) the physician doesn't "kid" himself. The psychotherapy is meant for the patient, not the physician.—Ed.]

Nonsurgical Orthopedic Measures. Such measures are aimed at keeping joints as free from pain as possible, at preventing flexion deformities and at maintaining normal motion.[523, 1650] Simple plaster splints aid greatly in preventing deformities and should be employed early while medical measures are being instituted. During acutely painful stages plaster molds are indispensable but must be removed at least once daily to allow motion.[116, 784, 1750, 1754] Warning was given against prolonged splinting to the point of marked atrophy of muscle and bone.[1601, 1644] For flexion contractures "coaxing methods," not brute force, should be used.[576] Flexion contractures of knees can often be corrected by a series of posterior plaster shells [360, 561]; traction and manipulation, wedging casts and forceful stretching are ineffective [sometimes—Ed.] and often harmful.[1043] Special splints for correction of deformities of various joints were described.[192, 164, 926, 1750, 1800]

Surgical Orthopedic Procedures. Kuhns and Dickson [1043] reviewed the indications for surgical procedures to correct flexion contractures of knees: manipulation under anesthesia for mild deformities due to capsular contractures without serious joint damage; posterior capsulotomy for resistant flexion contracture with little destruction of articular surfaces; osteotomy for fixations in bad position for weight-bearing and with extensive destruction of joint surfaces; arthroplasty for joints with bony ankylosis; arthrodesis for severely destroyed joints with persistent pain on weight-bearing in patients who must stand at work and for whom stability is more important than movement. Treating contracted knees, Kuhns [1043] obtained good results from posterior capsulotomy in 40 per cent of cases, from osteotomy in 33 per cent, from arthroplasty in only 10 per cent. Synovectomy was sometimes done for persistently swollen boggy knees without extensive articular destruction.[360, 561, 1384] Excellent results were obtained in 50 per cent, definite improvement in 20 per cent, of 64 cases in which synovectomy was performed by Dickson. Less promising results were reported by Ghormley and Cameron; excellent results were obtained in only 16 per cent, some improvement in 41 per cent, poor results in 40 per cent of cases; at the time of review the remaining 3 per cent had died. This procedure can be done while the disease is still active (Key [994]), but arthroplasty should not be done until the disease has become quiescent.[758, 793, 992, 994] Arthrotomy and joint lavage were recommended by two British authors (Bastow [85]; Fischer [561]). Technics for posterior capsulotomy were outlined.[1410, 1445] Total excision of the patella in four cases (combined with synovectomy in three and with posterior capsulotomy in one) gave notable relief of pain in three.[1981] Vitallium cup arthroplasty for persistently painful hips was discussed.[139, 926, 1680] Results in 10 cases reported from the Mayo Clinic were: "very good" in 40, "good" in 10, fair or poor in 50 per cent.[139]

Surgical procedures for correction of deformities of joints of upper extremity were described.[408, 793, 994, 1522, 1644] Smith-Petersen, Aufranc and Larson [1644] condemned such statements as: "wait until the acute condition quiets down"; "don't operate during the acute stage." They advocated earlier surgical intervention and de-

scribed such procedures as acromioplasty to relieve pain from associated secondary subacromial bursitis; excision of radial head for deformities of elbow; arthrodesis with excision of the distal end of the ulna for deformed wrists. Hass [793] reported good results from arthroplasty of the elbow with restoration of motion in eight (53 per cent) of 15 cases. Arthroplasty for small joints of hands and feet, with tantalum between the joint surfaces, was reported.[408] A patient with bilateral ankylosis of temporomandibular joints obtained an excellent functional result from excision of the heads of condyles.[470] On one side a graft of muscle and temporal fascia was used to fill the defect; on the other side no graft was used; resulting function on the two sides was the same.

Sympathectomy. Lumbar sympathectomy does not affect the course of rheumatoid arthritis (Key [994]). In dogs the increased blood flow which follows sympathectomy gradually becomes reduced after nine or 10 years to approximately that of the control or innervated side. This is due to hypertrophy of the muscular coat of the arteries on the denervated side.[537]

Prognosis in Rheumatoid Arthritis

Regardless of the treatment used, Cutts found that 59 per cent of private patients and 53 per cent of clinic patients tended to improve definitely. About a fourth showed marked improvement approaching a cure; half showed slight or moderate improvement; a fourth failed to improve or were worse. Cecil wrote [305]: "Certainly a considerable number of patients with rheumatoid arthritis have remissions during which they are free of pain and swelling in the joints. These remissions are likely to come fairly early in the course of the disease and sometimes last for several years. Patients who have had rheumatoid arthritis for five to six years rarely get natural remissions. When the disease becomes inactive at this late stage, it seems quite natural to assume that it results from some particular form of therapy."

So-Called Infective Arthritis

Some writers [567, 1392, 1596] distinguished between rheumatoid arthritis and the acute polyarthritis which follows in close temporal relationship to the development of an obvious focus of infection (sometimes called "focal infection arthritis," "postinfectious arthritis" or "infective arthritis"). In such cases articular involvement tends to be asymmetrical; large rather than small joints are predominantly affected; there is little or no tendency to progression; a chill and fever (102 to 104° F.) may occur at the onset; the sedimentation rate is markedly elevated and polymorphonuclear leukocytosis is present; the disease is self-limiting; the prognosis is better than in rheumatoid arthritis. [Five of us believe that this is just a variety of acute or subacute febrile rheumatoid arthritis; others of us do not agree.—Ed.] Pilot [1392] concluded that hemolytic streptococci usually can be found in the focus and that whereas removal of tonsils and diseased teeth are of "little value in rheumatoid arthritis," a marked and often dramatic therapeutic response usually occurs in "focal infection arthritis."

Still's Disease and Felty's Syndrome

The literature on Still's disease (juvenile rheumatoid arthritis with splenomegaly, lymphadenopathy and anemia) was reviewed by Angevine who reported

six cases. Objective manifestations and the histopathologic findings in joints are identical with those in adult rheumatoid arthritis. Deformities appear earlier; demineralization occurs more rapidly and is usually more extensive; crippling and muscular wasting is greater as a rule; subcutaneous nodules are rare. But nodules were described by Field [556] in one case. Eleven other cases of Still's disease were reported [43, 410, 1368, 1808]; in one case Still's disease of three years' duration was complicated by diffuse amyloidosis. The original article on Still's disease, "On a form of chronic joint disease in children," was reprinted as a memorial to the late George F. Still.[1727] Some [1704, 1709, 1767] would discard the term "Felty's syndrome," because it does not indicate a specific entity but rather a rare type of rheumatoid arthritis in adults associated with splenomegaly and neutropenia. Additional findings at times were hepatomegaly, lymphadenopathy, tachycardia, anemia, fever, cutaneous pigmentation, eosinophilia and monocytosis.[794, 1117] The cause of the leukopenia and anemia remains uncertain. According to Steinberg [1704] they are not due to depression of bone marrow: in two of his three cases the sternal marrow was studied and hyperplastic bone marrow with marked erythropoiesis and myelopoiesis was found. This type of marrow was considered identical with that in rheumatoid arthritis.

Although splenectomy has been advised for "Felty's syndrome," in no patient so treated have the beneficial effects on the anemia and leukopenia been more than transient; the postoperative course usually has been characterized by general decline (Hatch [794]; Waitzkin). [Decline and death a few months after splenectomy have been reported in several cases.—Ed.]

Osteoarthritis: Degenerative Joint Disease

Following the British nomenclature adopted by the American Rheumatism Association, most writers now refer to "osteoarthritis" rather than "hypertrophic arthritis." Short and Bauer [1600] preferred the term "degenerative joint disease" because it does not imply the presence of inflammation and spares patients the fearsome term "arthritis." For the same reason Neligan preferred the term "arthrose." But some of the pathologic changes in osteoarthritis "meet the criteria of a chronic inflammation" (William Bauer [96]; Goldberg [662]).

The clinical distinctions between primary and secondary osteoarthritis were upheld,[1441, 1600] but both types give the same roentgenographic and pathological picture in affected hips.[761]

Primary Osteoarthritis (Hypertrophic, Senescent, Degenerative Arthritis)

Incidence. Degenerative joint disease is the most common articular disorder.[1008] All persons beyond the second or third decade of life exhibit degenerative changes in joints,[724, 1600] but skeletal symptoms rarely occur before the age of 40 years.[968, 1040] According to Howell "rheumatism" is not an inevitability of old age: among 400 males more than 65 years of age only 35 had symptoms of "rheumatism," of which only six had osteoarthritis sufficient to require treatment; fibrositis was more common. Due to the preponderance of younger men in the army, only 7.5 per cent of the rheumatic patients admitted to an army general hospital in 1942 had osteoarthritis (Boland).

Special Clinical Features. Pain in the arm with paresthesias in fingers from cervical osteoarthritis was again described (Kelly [870]). Pain in a shoulder from osteoarthritis of acromioclavicular joint was relieved by roentgen therapy (Oppenheimer [1320]). A synovial cyst of the skin (a rather rare lesion which may accompany Heberden's nodes), after injection of a contrast medium, was found by roentgenograms to be connected with the joint cavity. Hence Eliassow and Frank concluded that such synovial lesions of skin are "due to an escape of synovial fluid from the joint cavity." Acroparesthesia commonly accompanies Heberden's nodes.[2350]

More attention is being paid to osteoarthritis of temporomandibular joints.[96, 289, 1203, 1558, 1588, 1600, 1848, 1931] Short and Bauer [1600] listed the many symptoms which may result from osteoarthritis of this joint (symptoms sometimes referred to as "Costen's syndrome"). These include deafness, tinnitis, earache, dizziness, nystagmus, headache, herpes of the external auditory canal and buccal mucosa, and burning or dryness of mouth or tongue. Erosion of the bony portions of this joint have been thought to affect hearing but Shapiro and Truex could not prove this. About 100 rice bodies were removed from an osteoarthritic temporomandibular joint.[239]

Pathology. Pathologic studies of surgical and necropsy material indicated to Goldberg [662] that cartilage erosions occur simultaneously on both opposing surfaces of an articulation rather than erosion on one surface being accompanied by corresponding overgrowth on the opposing surface as has been taught. Magnuson described two forms of cartilaginous degeneration: one starts at the surface and progresses toward the matrix, the other starts at the matrix and progresses toward the surface. In the first type, surgical removal of the degenerated tissue was followed by hyaline regeneration provided the process had not extended through the whole thickness of cartilage; in the second, hyaline regeneration did not occur but the defect was filled by fibrocartilage which seems to serve as an adequate covering to prevent friction. In articular cartilage of cattle a definite progressive diminution of cellular density occurs with age.[1859] Impairment of oxidative activity of old cartilage cells was noted also and suggested that the changes incident to age result from the inability of the numerically reduced cells to "breathe" properly.

Laboratory Data. Liver function, measured by the hippuric acid test was subnormal in five of 15 cases.[823]

Etiology and Pathogenesis. 1. Factor of Trauma. Confirmation of the generally accepted idea that long-continued minor trauma is the most important etiologic factor [1892] was found in Magnuson's work on dogs.

Various types of gross damage to cartilage, injections of irritating chemicals and bacterial toxins, and introduction of foreign bodies failed to produce proliferation of bone or degeneration of cartilage in regions other than those immediately involved. Typical degenerative arthritis was produced experimentally only one way: by allowing the animal to subject the joint to oft-repeated slight trauma. This was done by cutting medial and crucial ligaments to render joints unstable and then allowing the dogs to run freely. Typical exostoses formed in six to nine months and appeared before significant degeneration of cartilage was noted. Magnuson concluded that human degenerative arthritis probably results likewise from repeated small trauma. "It may be aggravated by low-grade infection or chemical or metabolic toxemia. Once roughening is established, the mechanical irritation of this roughening is sufficient for

prolongation of symptoms and disability." [Excellent colored photographs accompanied Magnuson's article.—Ed.]

2. Factor of Heredity. A familial tendency for the development of Heberden's nodes was statistically demonstrated by Stecher and Hersh.[1693, 1694]

Among 68 families of patients with Heberden's nodes the mothers of such patients were similarly affected twice as often, the sisters three times as often as the general female population. The incidence of Heberden's nodes in the general population was as follows: in females 2.6 per cent at the sixth decade (50 to 59 years of age) increasing to nearly 30 per cent in the ninth decade; in males from 3.6 per cent in the sixth decade to 8.4 per cent in the eighth. Through all age groups the sex ratio is 10:1. Despite an apparent lack of agreement with mendelian ratios, the data suggested that the genetic mechanism involved a single autosomal gene, sex influenced, dominant in females, recessive in males. This conclusion is not now directly applicable to other forms of osteoarthritis.

3. Factor of Impaired Circulation. Of 71 osteoarthritic patients 23 (32 per cent) presented arterial spasms, but only 32 per cent of 86 "controls" (patients with advanced organic arterial disease) had evidence of "rheumatic or arthritic involvement" (Steinbrocker and Samuels [1708]). "Pronounced arterial disease alone does not usually produce arthritic signs and symptoms."

4. Factor of Neuroendocrine Dysfunction. Pemberton and Scull [1364, 1370, 1371, 1372, 1373] consider both osteoarthritis and rheumatoid arthritis basically metabolic disorders due to an "imbalance of the neuroendocrine system" which "involves several links of the system rather than a single outstanding dislocation."

5. Factor of Gastrointestinal Dysfunction. Roentgenographic abnormalities of gastrointestinal tract, especially in colon, were found by Pemberton more often in cases of osteoarthritis than in rheumatoid arthritis. No one abnormality was characteristic. It was not determined whether they are the cause of, or the result of, the arthritis.

[They may not be either; they may be coincidental.—Ed.]

6. Factor of Infection. Almost as many infected foci were found by Bach [49] in 77 cases of osteoarthritis (total 276 infected foci; average 3.5 for each patient) as in 99 cases of rheumatoid arthritis (total 428 infected foci; average 4.3 for each patient). Regardless of their etiologic rôle Bach [49] believed they should be eradicated even in osteoarthritic patients.

Medical Treatment. For osteoarthritis the expression "active medical treatment" is less appropriate than "management" since unfortunately treatment is limited in scope and value and no new remedies of proved worth have appeared. "The obvious thing to do is to 'spare' the joints, just as one spares a horse that is 'a bit gone in the forelegs' or a car with a worn transmission." So wrote Neligan. "If the patient will cooperate, the wearing of his joint may be stopped; it will at any rate be slowed down." The usual measures were recommended: reassurance; rest periods; reduction of traumatizing excess weight; heat.[820, 1042] Of 158 patients with disabling osteoarthritic hips 30 per cent were "entirely relieved," 37 per cent greatly improved by various treatments, especially roentgen therapy or manipulations (Kuhns [1042]). Patients with osteoarthritic hips or knees should avoid living in hilly districts; those with affected hips who insist on hunting or riding "should get a pony with a small barrel." [1292]

Currently physicians seem to have an urge to make intra-articular injections into hips or knees with "good" results in the usual 60 to 80 per cent of cases

regardless of what was injected. Thus injections of 1 per cent acid potassium phosphate gave "lasting benefit" to 60 per cent of Crowe's [412] patients, and "temporary relief to all others." By "acidifying the joints" with injections of lactic acid of pH 5.8 Waugh again claimed relief in 70 per cent of patients so treated. Injections of 10 per cent benzyl salicylate improved 80 per cent of Elkin's [517] patients. Testosterone propionate presumably was of value in two of three cases of osteoarthritis in males.[715] Thyroid and estrogenic hormones were considered useful by a few.[324]

[Until these results have been confirmed we do not recommend such treatment. —Ed.]

Roentgen therapy to control pain [970, 1042, 1320, 1887] or mecholyl iontophoresis [779] were again recommended. A bedtime dose of quinine sulfate (3 grains; 0.2 gm.) will relieve night cramps in calf muscles, which occur so often in patients with osteoarthritic knees (Gootneck).

Surgical Treatment. Removal of loose bodies from osteoarthritic knees may be necessary to overcome mechanical locking (Colonna). Manipulation under anesthesia was used in selected cases.[820, 1042] Synovectomy, only rarely indicated, gives good results in selected cases (Ghormley and Cameron). Cheilotomy, simple excision of osteophytic fringes of long spurs around acetabular margin or femoral head, may be a useful, though often temporary, expedient.[360] Arthrodesis is the surest way to relieve painful hips,[639, 733] but few patients are willing to accept an ankylosed hip. In selected cases excellent results with resultant movable joints may be obtained from cup arthroplasty.[139, 639, 763, 766]

Recently reported were results from cup arthroplasty obtained by Bickel, Ghormley, Coventry and Mussey in 27 cases of osteoarthritis of hips, sometimes of the primary (idiopathic, senile) type but generally of the type secondary to congenital anomalies, Legg-Perthes' disease and so forth. Results eight months to five years after operation were as follows: in 15 per cent results were "very good": the patient was able to walk without support and had good motion of the hip with no noticeable limp or pain. In 30 per cent results were "good"; pain was absent or minimal; the patient could walk well on the level and on stairs, although at times a cane was required. In the remaining 55 per cent results were only fair or poor. Results were better among men than among women. Cup arthroplasty was recommended by Ghormley,[639] not for hips that are merely painful, but in cases in which much limitation of motion is also present. It was not recommended for patients more than 60 years of age.

Cup arthroplasty was done by Harmon [763, 766] on 16 hips of 13 patients. Results 18 months later follow: "excellent" in 10 hips (62 per cent); "good" in three (19 per cent); poor in three (19 per cent).

Although hips or knees were joints usually so treated, a satisfactory tantalum cup arthroplasty of a first metatarsophalangeal joint in a wounded marine was reported (Crosby and Galasinski). Harmon [763] treated metacarpophalangeal and temporomandibular joints with small plastic cups with excellent results "in all cases." [Numbers not stated.—Ed.]

Vitallium cups, superior to lucite cups, were generally used.[139, 642, 1680, 1804] But Harmon [763] preferred cups of methacrylate plastic which permit postoperative roentgenographic visualization of joints.

Apropos of the introduction of metal (cups or nails) into joints Neligan asked: "Does metal in a hip joint contraindicate the use of diathermy?" A patient whose fractured hip with traumatic osteoarthritis was treated by nailing was, a year later,

"convinced that she had had very much more pain after she had had a few (diathermy) treatments."

[According to Dr. Frank Krusen, physiatrists apply diathermy with caution or not at all to a region containing implanted surgical metals. Recent studies by Pudenz, Gersh and Etter indicate the comparative safety of the procedure, at least when the metal is implanted in tissues having a normal supply of blood. But Krusen agreed with Lion (1947) that diathermy should always be applied with caution over regions containing implanted surgical metals.—Ed.]

Postoperative exercises are a principal factor in results obtained from reconstruction operations (Preston [1409]).

Patellectomy, recommended for osteoarthritis of knees by Tippett (1938) and Berkheiser (1939), was done by Young and Regan [1981] when painful motion (even without weight-bearing) was presumably due to a mechanical impediment to function. Total patellectomy, sometimes bilateral (with or without cheilotomy), was done in 14 cases of osteoarthritis: results were excellent in seven, good in four, fair or poor in three. In nine cases pain was relieved completely. The operation "permits a good range of motion, diminution of pain and a surprisingly stable knee" (Colonna). Opinions differ as to the relative functional importance of the patella.[1981] Although the patella is being removed to help osteoarthritic patients, experimental tibiofemoral osteoarthritis can be produced in rabbits by total patellectomy.[354] [Indications for total patellectomy have not, in our opinion, been clearly defined, nor can final conclusions on its value be determined from the few cases reported to date.—Ed.]

Secondary Osteoarthritis

The causes of secondary osteoarthritis of hips were listed by Ghormley [639] and Harmon.[763]

They included: (1) for juveniles and adolescents, coxa plana (Legg-Calve-Perthes' disease); slipped upper femoral epiphysis; septic arthritis (with or without dislocation); childhood arthritis (Still's disease); congenital dislocation; congenital aplasia of acetabulum; congenital anomalies of upper part of femur; coxa vara of other types (rickets, osteomalacia); (2) for adults, injury followed by aseptic necrosis of femoral head; fracture of pelvis into acetabulum; fractures of femoral neck; traumatic dislocation complicated by late avascular necrosis; rheumatoid arthritis; septic (suppurative) arthritis; protrusio acetabuli (Otto pelvis) traumatic or infectious in origin; Paget's disease of pelvis and upper part of femur; Caisson disease; chondromatosis; osteochondritis dissecans; syphilis (painless "Charcot's hips").

(For other data on secondary osteoarthritis see the section on "Diseases of Joints Related to Trauma.")

Backache and Sciatica

More than 500 papers on backache appeared during the period under review; many described proper methods for taking histories, special physical examinations and roentgenographic studies of patients with backache.[205, 419, 453, 620, 640, 641, 851, 904, 913, 1214, 1284, 1688, 1720, 1759, 1932, 1945, 1976, 1984, 1986]

Backache from Lumbrosacral and Sacroiliac Sprains and Strains and from Sacroiliac Subluxations. No new, precise criteria were described for the diagnosis of these vague conditions.[48, 208, 364, 929, 930, 931, 1214, 1258, 1265, 1415, 1871, 1984]

Symptoms which indicated lumbosacral or sacroiliac sprains or sacroiliac subluxations to some writers seemed much like those set forth by others as symptoms of protruded disks.

Flexion-strains of spines of cadavers applied by a screw machine produced rupture first of intertransverse ligament and quadratus lumborum fascia, then of annulus fibrosis and adjacent ligaments, and finally of supraspinal ligaments and intervertebral disks.[723] Strains due to "imbalance between the capacity of structures of the back and the physiologic demands made upon them" were again blamed for most low back pain.

Treatment of back strains should be the same as that of muscular or ligamentous tears elsewhere in the body: the injured structure is placed in a position of relaxation (by rest in bed, physical therapy, plaster shells, back supports) until healing is at least partially completed (Kuhns [1041]). Local injections of anesthetics and manipulations were recommended for acute strains.[38, 565, 929, 930, 931, 1603]

Industrial Backache. Backaches in industrial workers, "the bane of the industrial medical practitioner," are often characterized by disability greatly out of proportion to physical findings.[973] Compensation factors confuse the picture.[65]

The high incidence of this condition was shown by the fact that in one steel plant in one year there were 190 claims among 3,700 workers.[1214] To reduce such claims other workers were instructed how to lift heavy objects; the result was that during 10 years an average of only five weeks yearly was lost by a group of 2,200 workers.[1280]

Gradual physical rehabilitation effectively reduced time lost from work because of back injuries.[479, 922] Patients were first given light work, then gradually returned to former occupations. Thus 92 per cent of persons with "acute industrial backs" returned to work within five days. Industrial workers with compensable back injuries involving protrusion of disks or hypertrophy of ligamenta flava had excellent results from surgery and returned to work as early as did nonindustrial workers.[502]

Postural Backache. A few writers discussed lame backs caused by faulty posture.[265, 641, 1072, 1114, 1795, 1993] In this condition backache develops after standing or hard work, is relieved by rest, and does not interfere with sleep. The patient is free from pain in the morning on arising. It is a fatigue phenomenon. Treatment includes postural exercises, regulated rest, physical therapy and supports.[265, 1255, 1258, 1795, 1984, 1993] The patient's understanding and cooperation are essential; he must devote much time and effort to overcoming his defect and can obtain good results only if he is willing to use graduated exercises for a long time.[641]

Backache from Tight Fascial Bands. Fasciotomy of iliotibial band was again recommended for the relief of contractures.[1309, 1311, 1387, 1945] Of 86 patients so treated 41 had excellent results, 33 were improved, 10 were not significantly improved. Conservative measures, often successful, should be used before surgery is undertaken.[1309]

Another form of fasciotomy was recommended: subperiosteal stripping of ligaments, muscles and fascia from their attachments to the posterosuperior spine of ilium and posterior third of the iliac crest (Heyman). Certain patients with backache "unrelieved by usual orthopedic measures" were treated with either or both these types of fasciotomy which were regarded as supplements to conservative therapy.[736]

Backache from Spondylolisthesis. Among Meyerding's [1233, 1234] 745 patients with spondylolisthesis were 80 (10.7 per cent) with backache and also sciatica. The latter presumably was caused by a prolapsed disk as was proved by operation in six cases (removal of disk and spinal fusion).[1233, 1234] All symptoms associated with spondylolisthesis were attributed by Dandy [430] to "defective intervertebral disks." "The end

result of removal of disks was fusion of the opposing vertebrae and stabilization of the spine"; bone grafts were unnecessary.

Spondylolisthesis is generally developmental but may result from injury. Three traumatic cases were noted: vertebrae with the laminar defects were not displaced as is usual in developmental cases; slipping took place at the body below the defect (Kleinberg and Burman).

Backache from Reverse Spondylolisthesis. No new data appeared.

Backache and Sciatica from Primary Sciatic Neuritis. Fifty-five cases were reviewed [21]; most (67 per cent) were in males doing muscular work and exposed to changes in weather. The incidence was highest between the ages of 30 and 60 years. The condition, which was generally self-limited, lasted from one to 12 weeks, occasionally from a few months to five years. The distinction from secondary sciatica was based on finding of tenderness in nerve trunks and absence of abnormalities in spinal fluid. [We doubt the validity of this differentiation.—Ed.]

Backache with Osteoporosis. A study of 208 cases noted in the "Eighth Rheumatism Review" was reported in more detail.[145] Two new series were reported.[263, 1291] Acute or chronic pain was present in some, absent in others. While some patients were performing trivial movements, agonizing, sometimes "nauseating" pain, appeared low in the back. Some heard a crack, snap or "give" in the back. Loss of height was sometimes notable. Principal signs were kyphosis or kyphoscoliosis. In some cases oblique folds of skin ran downward and outward in the thoracolumbar region and a deep transverse abdominal furrow was present. Roentgenologic changes included osteoporosis, biconcavity, collapse, wedging, crushing, localized fractures of vertebral bodies and pseudarthroses between lumbar spinous processes.

Necropsies in three cases disclosed extreme osteoporosis, attenuation of cartilage plates separating the disks from the bodies, squat biconcave vertebral bodies and bulging nuclei.

Treatment included dietary supplements of calcium and vitamin D, and orthopedic supports (plaster bed for night use, and corsets or a steel and leather support for day use). Patients improved clinically but not roentgenographically. Five or six years [sometimes more—Ed.] of such treatment may be required before [if ever—Ed.] the skeleton regains its former calcium content.[263]

Backache from Hypertrophied Ligamentum Flavum. According to most writers on this subject diseased ligaments sometimes cause sciatica with symptoms like those of protruded disks.[572, 1260, 1334, 1425, 1976, 1977] Others disagreed.[288, 893, 1415]

When only hypertrophic ligaments were found, results of surgery were generally poor.[572] Histologic evidence of disease in the ligaments included fibrosis and breakup of laminations of elastic fibers, and replacement by collagen fibers, presumably from degenerative changes.[1095, 1219] The size and thickness of the ligamentum flavum seemed less important than histologic changes. Measurements were unreliable because of technical factors.

Backache from Metastatic Lesions. Features which permit diagnosis before roentgenographic evidence of metastasis appears were described.[356, 1355, 1805, 1969] Pain may be segmental and aggravated by coughing, sneezing, yawning, straining at stool, bending or sudden jarring. It is constant, unmitigatingly intense and not influenced by climatic changes. The patient is often reluctant to move

or turn. Percussion tenderness is a constant sign. But some patients with extensive spinal metastatic lesions are free of pain.[1805] [Backache requiring narcotics results usually from metastatic malignant lesions.—Ed.]

Backache from Urologic Lesions. Of certain patients complaining of backache 79 per cent had prostatitis and seminal vesiculitis,[1175] treatment of which relieved the majority. In 12 patients with hydronephrosis backache was the chief symptom.[1148]

Backache from Gynecologic Lesions. No new data appeared.

Backache from Gastrointestinal Lesions. Backache frequently results from diseases of the digestive organs.[1468] Penetrating gastrointestinal lesions caused acute, localizable pain, often limited to segmental distributions. Lesions in retroperitoneal tissues caused deep-seated pain which was severe and only fairly well localized. Metastatic spinal lesions produced boring, deep-seated constant and bilateral pain.

The Dorsolumbar Syndrome. This condition, also known as causalgic backache, was said to comprise a definite clinical entity in which pain occurs in lumbar muscles and extends along the twelfth rib.[881, 1622] The term "causalgia" was used because the pain is of a burning type. The syndrome was reproduced experimentally by elevating one heel: after three weeks the subject noted pain characteristically extending around the side as in dorsolumbar syndrome. Change of position and exercises caused the symptoms to disappear in two weeks.

The disease results spontaneously from injury or irritation of the quadratus lumborum muscle; the resulting contraction deflects the last rib downward and forward and thus increases the distance that the twelfth thoracic nerve traverses from its foramen to the subcostal groove. This produces painful tension in nerve sheaths, to relieve which the patient assumes a position of scoliosis.

Backache from Adolescent Kyphosis. This condition was said to result from destruction of nucleus pulposus before ossification of the vertebral body is complete. When this occurs, the weight-bearing function is transferred to the bodies anteriorly, and the axis of motion to the posterior vertebral joints; spinal flexion produces increased pressure at the anterior borders of vertebral bodies. If the patient is adolescent and the epiphysis is subject to trauma, abnormal ossification follows, leading to premature closure of the epiphysis, failure of ossification of the anterior portion of the vertebral body and wedge formation. Later the wedge-shaped bodies develop spurs at their anterior angles. The degenerated disk may ossify and bridges may form between spurs. Patients with this condition characteristically are stooped, have prominent abdomens and protruding necks. There may be scoliosis (MacGowan).

Backache from Spasm of the Levator Ani, Coccygeus and Pyriformis Muscles. These were described.[1924] Diagnosis was made by discovery of tenderness in the respective muscles on digital rectal palpation. Massage per rectum,[1924] infiltration of the first three sacral nerves with procaine,[1589] and section of the pyriformis muscle [596] were recommended.

Backache from Diseased Interspinous Ligaments or from Rickets. No data appeared.

Backache from Diseased Articular Facets. The inclination of sacral facets was found to average about 50 degrees from the sagittal plane: in 79 per cent of cases studied this did not vary more than 10 degrees; in 21 per cent the deviation was from 11 to 30 degrees. One out of five patients showed appreciable asymmetry associated with osteoarthritis (Badgley [80]).

An anatomic study showed that lumbosacral facets suffer from all the ills inherent to joints: degeneration of articular surfaces; thinning and fibrillation of cartilage; osteophytic marginal proliferation; detached chondral bodies; even

complete loss of cartilage. True subluxations of apophyseal vertebral joints may occur if there is narrowing of the disk between the vertebrae. To be significant, dislocation of facets must be sufficient to produce impingement on the pedicle above and on the lamina below, thus causing backache. At such a site a protruded disk also may be present.[50]

By injecting oil into the fourth and fifth lumbar apophyseal joints Larmon [1067] produced sufficient swelling to compress spinal nerves in the foramina: presumably arthritic swelling of these joints could similarly cause pain.

Technic for roentgenographic demonstration of lesions of facets was described.[1565, 1566]

Backache from Fibrositis. This will be described under "Fibrositis."

Backache from Congenital Anomalies. Low back pain was more frequent among persons with congenital anomalies of the lower part of spine than among others.[872, 1933] Some spinal anomalies strengthen the region; others decrease stability and predispose toward abnormally increased stress.

Psychogenic Backache. The general topic of psychogenic rheumatism is discussed later. Psychogenic backache has features which a history and physical examination will usually reveal and which permit accurate diagnosis, not just diagnosis by exclusion.

Symptoms complained of by patients with psychogenic backache were listed by Luck thus: (1) pain in coccyx extending up the spine to the thoracic region, neck or top of head; (2) pain not increased or relieved by any particular position; (3) pain not influenced by bending, lifting or lying down; (4) back pain not influenced or aggravated by rest or immobilization; (5) pain appearing near the coccyx or in wide areas of the back directly after healing of an organic low back lesion; (6) tingling and numbness in spine or extremities; (7) daily variations in the site of pain; (8) sensations as if part of the back were "missing" and "out of full control"; (9) feeling of a lump low in the back; (10) feeling of tension in the back that cannot be relieved; (11) constant throbbing in the back.

Although frequently absent, objective findings (when present) in cases of psychogenic backache may include (1) hysterical paralysis, (2) hypalgesia, (3) camptocormia, (4) diffuse tenderness, (5) vasomotor instability, (6) tachycardia, (7) apprehensiveness.[1130] Backache from psychic disorders was ascribed to powerful muscular contractions during dreams in some cases (Saul). Overtreatment of trivial back injuries may exaggerate psychogenic backache. "The overly enthusiastic, talkative physical therapy technician suggesting a curvature of the spine here, a spasm in the muscle there, or the presence of painful nodes, is a menace in any back case" (Mock).

Psychogenic backache alone or aggravating organic diseases frequently affected soldiers during World War II (Boland and Corr). Such psychogenic disturbances interfered notably with recovery from organic types of backache. Successful treatment required the combined efforts of internists, physical therapists, orthopedists and psychiatrists. Treatment included postural exercises, use of charts and diagrams illustrating the dynamics of posture and supervised relaxing activities (Fox [581]). [It also should include psychotherapy.—Ed.]

Backache and Sciatica from Osteitis Condensans Ilii. This disease produces a symmetrical sclerosis of the ilium adjacent to the lower portion of the sacroiliac joint. The patients suffer recurrent attacks of low back and pelvic pain, usually worse on one side than on the other. In eight of 23 cases, onset of symptoms occurred prior to or following delivery, and all the patients were women of childbearing age. The sedi-

mentation rate was normal in 21, elevated in two; other laboratory tests were negative. There was no tendency for the process to progress to involve the vertebral joints.[755] [Could these cases represent localized rheumatoid sacroiliitis?—Ed.]

Miscellaneous Causes of Low Back Pain. The following conditions causing low back pain with or without sciatica were described: spinal epidural abscess [165, 239, 240]; functional disorders of the foot; "nipping of soft tissues" between ribs and pelvis [1991]; backache of "reflex origin" [893]; functional decompensation of back [796]; backache due to downward subluxation of fifth lumbar vertebra on sacrum [209, 210]; subarachnoid hemorrhage [1542]; Paget's disease; hemangioma of vertebrae [146, 551]; endocrine disorders.[891]

Backache and Sciatica from Diseased Intervertebral Disks

Over 200 papers were reviewed; only a few can be mentioned.

The anatomy and pathology of intervertebral disks were studied.[200, 398, 513, 894, 1257, 1265, 1321, 1323, 1421] The belief that expansile qualities are possessed by disks was considered erroneous.[200, 474, 1470] Disks were said to be plastic but not expansile. [Others still insist they are expansile.—Ed.] The cushion-action of the disk is due to its passive distortion as a result of muscular action on spine, not to actual compression of the nucleus. Roberts [1470] regarded an essential tonus of the annulus as the pressure-producing agent, but Doel considered this impossible and attributed the compression to muscle tone, gravity and atmospheric pressure.

By analyzing the force vectors which result from lifting a weight of 50 pounds (22.7 kg.), it was estimated that pressure of 500 pounds (227 kg.) is exerted against the lower lumbar disks. When the spine is flexed, the nucleus pulposus migrates dorsally, tension is thrown on the posterior portion of the annulus, and the annulus may be subjected further to torsional stresses. These considerations were believed responsible for the high incidence of posterior protrusions of lumbar intervertebral disks.[894]

Acute Infectious Lesions of Intervertebral Disks. No new data appeared.

Calcification of Intervertebral Disks. In adults, especially the elderly, calcification of disks occasionally accompanies degenerative changes (Albert [15]); rarely it may be caused by ochronosis (Freund [599]; Hertzberg). In childhood the condition is rare, probably the result of infection; such a case was reported (Weens).

Spinal Puncture Injuries. Collapse of a disk with narrowing of intervertebral space and marginal proliferation sometimes follows injury by spinal puncture needles.[481, 528, 540, 1594, 1722, 1742] Needles inserted into the subarachnoid space were studied roentgenographically and were frequently seen in a position where further insertion could have resulted in puncture of the annulus fibrosus and possible damage to the nucleus.[1272]

Ruptured Intervertebral Disks. 1. Cervical Region. Ruptured fifth, sixth, seventh and eighth cervical disks produce characteristic syndromes of pain in the neck extending into certain regions of shoulder, precordium and hand. These syndromes were described.[220, 248, 355, 439, 520, 1237, 1286, 1580, 1687, 1733] The picture may simulate that of coronary occlusion, scalenus anticus syndrome, cervical rib or brachial plexus neuritis.

Although the diagnosis of protruded cervical disks at times may be made without myelograms,[829] opaque oil myelography was considered a valuable diagnostic adjunct. With care, the oil can be prevented from entering the cranial cavity. When some accidentally entered the skull, no untoward results occurred.

Protrusion of intervertebral disks may result from "recoil injuries" in which the

cervical part of the spinal cord is severely damaged without demonstrable or commensurate roentgenographic evidence of injury to the spinal column.[404] Herniation of an ossified cervical nucleus pulposus caused complete transverse myelitis in one case.[217]

2. Lumbar Region. Many new cases were reported. Usually symptoms of protruded lumbar disks result from pressure on nerve roots. When protrusions are massive, symptoms resembling those caused by compression of cord may result. This may readily be mistaken for tumor.[445, 541, 598, 1852]

In one case a protruded lumbar disk produced complete spinal block (Froin's syndrome).[882] Four cases of maternal obstetrical paralysis and so-called neuritis of pregnancy or the puerperium with paralysis of one or both lower limbs were attributed to protruded disks.[1313] Relaxation of pelvic ligaments during delivery may predispose to protrusion of a disk.

3. Diagnosis. Special neurologic tests and diagnostic maneuvers were described and illustrated.[77, 192, 501, 688, 798, 1059, 1126, 1271, 1383, 1403, 1404, 1415, 1418, 1597, 1634, 1851] A new dermatome chart of lower extremities was useful in localizing protruded disks without the aid of myelograms. Keegan [960, 961] prepared it by studying hypalgesia resulting from proved single lesions of nerve roots caused by protruded disks. The locations of dermatomes in this new chart differed from the classic patterns described in textbooks on anatomy.

Many negative explorations for suspected disks were attributed to "concealed disks." [426] The disk bulges so slightly that it is not disclosed by iodized oil and can be found at operation only by careful inspection. Symptoms are like those of protruding disks. Pains were attributed to adhesions to the nerve, rather than to mechanical pressure. Proper treatment requires removal of disk.

Diagnosis of herniated disk as distinct from torn or degenerated disk was made by Young [1985] on a combination of signs which he called "the compression syndrome"; pain on standing flexion, pain on extension, pain on flexion to the sound side, and deformity either in forward flexion, or flexion to the sound side, or both. Characteristics of "nerve root pain" caused by protruded disks (or other diseases affecting sensory nerve roots) included (1) intensification on sudden increase in intra-abdominal and intrathoracic pressure, and (2) intensification by bending the head forward, stooping, straight leg raising, the Lasègue maneuver and spontaneous elongation of the spine during sleep (Eaton [497]).

The diagnostic value of contrast myelography with the use of air,[8, 201, 453, 1060, 1431, 1548, 1563, 1964] oxygen,[756] lipiodol,[177, 529, 893, 1038, 1423, 1688, 1964] thorotrast,[202, 253, 1301, 1306] and pantopaque were reviewed. The 500 oxygen myelograms studied by Hare and Langs [756] were "85 per cent accurate." Although a positive finding in an air or oxygen myelogram was considered of diagnostic importance, the lesion could not be detected in all cases by this means. A normal, air or oxygen myelogram was not sufficient for ruling out a ruptured disk. Succeeding injections of lipiodol sometimes revealed pathologic processes. Headache, following air myelography, may be severe and incapacitating.

Advantages and disadvantages of thorotrast were discussed. An alkaline buffered suspension of thorium dioxide in a protective colloid, dextrin, was used. This has a low viscosity which permits almost complete removal from the subarachnoid space by forced spinal drainage. Its radioactivity is supposedly not sufficient to produce pathologic effects. Excellent contrast roentgenograms were obtained thereby but the time-consuming procedure of continuous spinal drainage necessary for its removal was a serious objection.[1688] It was considered dangerous by Bradford [202]: in one case signs of meningitis developed after its use.

Lipiodol was considered reasonably safe, but most writers agreed that lipiodol should be removed after roentgenograms are made. Technic for removal of lipiodol was described.[942] Its removal may be sometimes difficult and incomplete.

The new contrast medium, pantopaque, introduced by Steinhausen and colleagues, is a mixture of isomeric ethyl esters, the principal constituent of which is ethyl iodophenylundecylate. It casts an excellent shadow in roentgenograms but is not so opaque that it obscures fine gradations of density. Its use in diagnosis of protruded disks was described.[36, 117, 386, 494, 498, 1469, 1555, 1678, 1688] It is absorbed slowly. (Lipiodol is not absorbable.) It is stable in solution, not miscible with spinal fluid and is nontoxic. All but a few drops can be removed and in most patients in whom it was allowed to remain no ill effects were suffered. But Schnitker and Booth noted three patients among 100 studied with this agent, in whom symptoms of meningismus with elevation of cell count and total protein of spinal fluid resulted.

False-positive contrast myelograms may result from (1) bulging of the entire disk without herniation, (2) backward and downward settling of a vertebra due to degeneration of a disk with narrowing of interspace, or (3) forward projection of the ligamentum flavum because of proliferation of margins of underlying facets (Horwitz). These may cause discrepancy between roentgenographic reports and operative findings. Dandy [426] objected to the use of all contrast media for localization and diagnosis of protruded disks, believing this should be accomplished by clinical findings alone with "almost absolute accuracy." [Others disagreed and believe that contrast myelograms are useful in diagnosis when properly employed.—Ed.]

A new method for detecting and localizing protruded disks involved study of roentgenograms made while the patient performed extension, forward flexion and lateral flexion to both sides.[488, 1023] A somewhat similar plan was described by Gianturco: tracings of spinal roentgenograms made with the patient in the erect and in the forward and backward flexed positions were superimposed. The method was applied especially to lesions in the fourth and fifth lumbar interspaces. Abnormal motions were recognized for which disease of the disk was commonly responsible. No conclusions were reached regarding practical application of these methods.

New maneuvers for physical diagnosis of protruded disks were described. The patient lies supine with knees flexed over the end of the examining table in order to increase the lumbar lordosis. In this position sacral and lumbar roots are relaxed. But the pincer action of hyperextension tends to increase the protrusion of the disk. In a typical case, there is first a latent period followed by steadily increasing peripheral pain. Upward pressure on the painful leg with traction on the painless leg produces pain which also appears after a latent period (Duncan and Hoen).

Narrowed intervertebral spaces do not necessarily indicate the presence of protruded disks. Many instances represent congenital anomalies at the lumbosacral junction. Narrowed disks were found in three (1 per cent) of 300 children between the ages of five and 15 years. None had any evidence of fracture, infection or trauma. The condition probably represented sacralization of the fifth lumbar vertebrae. Six cases were reported in which narrowed lumbosacral interspaces were noted in association with low back pain caused by other lesions (Vinke and White).

Treatment of Protruded Disks. The proper treatment of herniated disks will be debated for years to come (Poppen [1404]). Conservative management is usually preferable as recovery without operation ensues in a large proportion of cases. Once herniation of a lumbar disk has developed, the patient should always protect his back from undue stooping, lifting and strain. Operation should not be expected to restore a pathologic disk to normal.[961] Surgery should be used

when conservative treatment is unsuccessful, but ultraconservatism should not be practiced. When satisfactory progress is not being made after a few weeks of rest in bed, traction, use of casts, brace or belt or when a clear diagnosis of large complete herniation can be made, surgery is indicated.[961] Continuing intolerable pain or damage to nervous structures also provides justification for operation.

When operation is indicated the complete removal of all the degenerated cartilage was advised. Care should be taken to detect and treat multiple lesions if present. Operations currently in use do not significantly alter the supporting structure of the back and yield good results in most cases.[201, 499, 1126, 1597, 1851, 1911]

In advance of operation, a decision should be made as to whether spinal fusion is indicated. Although indications for fusion are not precise, most writers believe that fusion should be done when complications are present, such as spondylolisthesis or other anomalies which may cause instability.[77, 453, 543, 572, 1333, 1404, 1423, 1474, 1597] Dandy [427, 428, 429] believed that fusions are never indicated but Farrell and McCracker [543] considered results of fusion alone as good as those from laminectomy.

Although most writers recommended excision of the offending disk at operation, Ecker [503] considered that small or moderate intraspinal protrusions responded to decompression of the nerve root, that is, removal of the articular capsule to which the lateral portion of the ligament is attached. This operation gave him results as favorable as those from removal of the disk.

Intervertebral Foraminotomy. Opening of the intervertebral foramen by removal of facets and their articular processes was recommended by Bankart [70] in cases in which (1) simple laminectomy failed to reveal protruding disks, (2) the disk space had collapsed completely, (3) "spine surgery with or without fusion" failed to relieve sciatica,[212] and (4) severe sciatica occurred.

Sciatica: General Comment

Sciatica is a symptom of many conditions, including: (1) lesions within the nerve itself, or its central connections; (2) irritation or compression of the nerve or its central connections from nearby disease, and (3) pain referred from disease in distant structures. Even hysteria may cause sciatica.[853] Many cases are caused by fibrositis according to Jackson.[904] [Difficult to prove.—Ed.] Sometimes no cause seems apparent even after exhaustive study.[20, 904] In one case sciatica was caused by an aneurysm of the sciatic artery which pressed on the sciatic nerve in the buttock (LeCocq).

Epidural or perineural injections of saline, metycaine or procaine were again recommended.[421, 675, 676, 980, 1162, 1782, 1985]

An anatomic study of the relation between the lumbosacral trunk of the sciatic nerve and the sacroiliac joint in cadavers was reported (Hershey [833]). This nerve trunk traversed the lower third of the sacroiliac joint. Hence lesions such as osteoarthritis (which was present in 25 per cent of the bodies studied) seemed capable of producing direct irritation of the lumbosacral trunk and sciatica.[833] [Presumably other forms of sacroiliitis (sacroiliitis of tuberculosis or rheumatoid spondylitis) could similarly cause sciatica.—Ed.]

Specific Infectious Spondylitis

For discussion see comments on spondylitis under "Tuberculous Arthritis," "Syphilitic Arthritis," "Brucellosis; Undulant (Malta) Fever" and "Typhoidal Arthritis."

Rheumatoid (Ankylosing) Spondylitis

Historical Data. The original papers by Bechterew, Strumpell, Marie and Leri, and others were reviewed (Dunham and Kautz).

Etiology. Trauma, exposure, focal and other infections, psychic strain, gonorrhea and preceding ill health are not the cause of the disease but are only provocatives; sometimes no provocative factor is found.[176] Brucellosis was considered by Goldfain [664] the cause of five typical cases of ankylosing spondylitis, indistinguishable from rheumatoid spondylitis except for the "quite positive skin, agglutination and opsonic index tests for brucellosis."

[That brucellosis may cause rheumatoid spondylitis, in contrast to localized Brucella spondylitis, remains to be proved. Possibly these five patients had brucellosis unrelated to a coincidental rheumatoid spondylitis. The cause of rheumatoid spondylitis remains unknown.—Ed.]

Incidence. Rheumatoid spondylitis is, contrary to general belief, a fairly common cause of backache in young men. Of 1,000 new "run of the mill civilian patients" two (0.2 per cent) [832] had this disease. It was more common among military personnel, and affected 5.2 per cent of 270 rheumatic British soldiers (Savage [1541]), 18 per cent of all soldiers with chronic backache at an American army general hospital.[176] It affected 120 (0.4 per cent) of 27,031 such patients seen by Dekkers.

The condition generally appeared in adults between 20 and 40 years of age.[568] Although 47 per cent of Fletcher's [568] 68 patients were females [far out of line with the usual sex incidence—Ed.], males in other series were predominantly affected, comprising 91 per cent of McWhirter's 168 patients, 87 per cent of Goldfain's 18,[664] all of the 20 patients of Dunham and Kautz [489] and all of the 100 soldiers seen by Boland and Present.[176]

Clinical Data. The usual symptoms, signs and laboratory data were considered.[59, 148, 176, 244, 489, 568, 608, 811, 832, 1212, 1444] Earliest symptoms were often insidious backache or transient sciatica, sharp pain or catches in buttocks or lower part of back, girdle pains, fatigue, gradual spinal stiffness. Spinal flexion may cause pain that extends into neck, jaw, thorax, substernal or precordial regions (Niehaus).

Small dilated intracutaneous veins of the chest wall are often associated with rheumatoid spondylitis. Such veins were noted by Burrett and Scherf in 70 per cent of patients with cardiac or pulmonary disease, in 69 per cent of those with such miscellaneous conditions as diabetes and peptic ulcer, without notable pulmonary or cardiac disease. Presumably the dilatation of these veins was caused by increased intrathoracic pressure from coughing and sneezing, or the presence of incompetent valves in the affected veins.

Four cases of paravertebral abscesses with *localized* ankylosing arthritis of the apophyseal joints at the level of the soft-tissue abscesses were noted by Oppenheimer.[1319] The abscesses, resembling carbuncles of neck or back, were present at the level, not below, the involved vertebrae. Vertebral ligaments were ossified but there was no osseous destruction. Presumably the abscesses were the cause, not the result, of a "localized form of Strümpell-Marie disease or ankylosing (rheumatoid) spondylarthritis."

[It is difficult to believe these were cases of true rheumatoid spondylitis. But it would appear that the abscesses did provoke localized (nonspecific?) pathologic reactions similar to those of the usual disseminated rheumatoid spondylitis.—Ed.]

Laboratory Data. The average concentration of fibrinogen in plasma was slightly but insignificantly higher (559 mg.) in spondylitic patients than in those with peripheral rheumatoid arthritis (520 mg.) (Mester [1224]). As a diagnostic aid Mester's test (leukopenia from intracutaneous injection of salicylic acid) was grossly unreliable (Green and Freyberg [696]). Calcium and phosphorus metabolism were normal in two cases.[1011]

1. Cerebrospinal Fluid. The spinal fluid protein was increased (45 to 121 mg. per 100 c.c.) in 29 per cent of 42 patients with rheumatoid spondylitis (with or without peripheral rheumatoid arthritis), in only 7 per cent of 59 rheumatoid patients without spondylitis.[1131] Abnormalities in colloidal gold-curves were less common: present in 15 per cent of the spondylitics, in 8.5 per cent of the rheumatoids without spondylitis. Concentrations of sugar and chlorides, and manometric pressures were normal. Because the spinal fluid abnormalities occurred four times as often among spondylitics as among those without spondylitis there seemed to Ludwig, Short and Bauer [1131] to be a relation between the abnormalities and the presence of the arthritic inflammation in spinal and sacroiliac joints. Perhaps they are "due chiefly to an increased permeability of the spinal-cord membranes as a result of their proximity to acutely inflamed articular tissues."

2. Roentgenograms. Sacroiliac joints are usually those first affected.[176, 489, 568, 811, 826, 1408] Earliest changes were blurring of the articular borders, increased density, spotty osteoporosis of juxta-articular bone; later narrowing of joint space; finally ankylosis with "honey-combed" appearance of the lower portion, and cystic caries of margins.

Roentgenologic evidence of involvement of apophyseal joints was considered an essential finding in rheumatoid spondylitis by Oppenheimer,[1318] but not by Boland and Present.[176] Sacroiliac involvement was present in only 60 per cent of Oppenheimer's [1318] cases in which early apophyseal changes were present and in only 86 per cent of his total 50 cases, in all of which characteristic apophyseal lesions were noted. Other lesions noted were rarefaction of vertebral bodies in 52 per cent (neither a constant nor an early sign) and ossification of vertebral ligaments in 50 per cent of all cases. Involvement of costovertebral joints or of pubic symphysis, ossification of muscles or tendons about the pelvis, and rarefaction of pubic bones were noted in certain advanced cases. Even when special technics for roentgenographic study were used Boland and Present [176] found lesions in apophyseal joints to be less definite and constant than those in sacroiliac joints. In none of their cases were changes in apophyseal joints found without accompanying evidence of sacroiliitis. When apophyseal changes were found, usually only a few scattered apophyseal joints were affected while intervening ones appeared normal.

Pathology. The pathologic changes in a spine studied at necropsy involved the apophyseal joints and the intervertebral symphyses (Freund [599]). Lesions in apophyseal joints were similar to those of rheumatoid arthritis of peripheral joints. In the vertebral symphyses the disks had been partially replaced by vascular connective tissue as a result of invasion from the underlying bone. At the margins of disks, ossification had taken place and true osseous bridges were found. This ossification of disk margins was considered responsible for the bamboo appearance. The intervertebral ligaments, which are generally considered to be the site of the pathologic process producing the bamboo appearance, were spared.

Treatment. 1. General. The use of rest, physical therapy, corrective exercises and orthopedic supports was reviewed.[59, 244, 489, 568, 926, 1655] Concentrated vitamin D was recommended by some,[1011, 1084] but not used by most writers.

2. Roentgen Therapy. Recommended for some years chiefly by Kahlmeter in Sweden, and Scott in England, roentgen therapy has not been used much in this country as yet. Although Smyth, Freyberg and Peck [1652] found it of little value in rheumatoid arthritis of peripheral joints, it gave notable relief in cases of rheumatoid spondylitis according to Smyth, Freyberg and Lampe.[1651]

Of 52 spondylitics so treated notable subjective improvement occurred in 72 per cent, notable objective improvement (increased chest expansion and spinal mobility) in 50 per cent, significant reductions in sedimentation rates in 41 per cent. Results were excellent for patients who had early spondylitis with the sacroiliac joints only involved: "In this group 92 per cent showed significant, sustained, subjective and objective improvement, and some were completely relieved of all clinical evidence of disease." To ascertain whether results were from psychotherapy certain patients were subjected to the ritual of roentgen therapy but, unknown to the patients, a lead screen blocked the rays. None of these patients obtained significant improvement "but without exception when they were later treated with roentgen rays significant improvement occurred."

The technic employed 200 kilovolts (175 kilovolts, constant potential equivalent) with 0.5 mm. of copper and 1.0 mm. of aluminum, a ½ value layer of 0.9 mm. of copper, a 50 cm. skin-target distance and an output of 50 r (measured in air) per minute with the site of the field approximately 200 to 300 sq. cm. In their first cases Smyth, Freyberg and Lampe [1651] treated each field three times with 200 r each time. Treatments were given every other day so that the total dose per field was 600 r. In later cases the doses were reduced to 450 r or to 300 r per field (150 r every other day). Usually three series were given to the same field with a month between each series. If symptoms were not completely relieved, or if symptoms developed in new sites additional treatments were given. The usual toxic reactions of roentgen therapy were observed: leukopenia, nausea and vomiting.

[Recently, to reduce the incidence of roentgen sickness, Freyberg [609] recommended an alternate scheme using lower voltages, wider and fewer portals and smaller doses of the rays (100 to 150 r for three treatments).—Ed.]

Roentgen therapy has since been recommended by many writers in America and England.[59, 148, 183, 359, 568, 811, 826, 848, 946, 1212, 1218, 1318, 1444, 1973] Good results were claimed both for the wide field, scattered roentgen-ray technic [148] recommended by Scott, and the concentrated local treatment method of Freyberg.[848, 946, 1318, 1444] A variety of technical factors were preferred by various writers; for these, reference should be made to the original papers.

When spondylitic women receive roentgen therapy, it should be given carefully with the proper use of filters to prevent sterilization.[811]

Although most observers noted no significant roentgenographic improvement after roentgen therapy, Oppenheimer [1318] noted "a surprising change" in the roentgenologic appearance in four early cases. Joint spaces, previously clouded and apparently filled with bone before treatment, were said to have become radiolucent and clearly defined after treatment. These patients were presumably cured as no recurrences occurred during 18 months of observation. [Not a certain cure.—Ed.] In advanced cases, the roentgenographic lesions were irreparable but roentgen therapy gave "considerable subjective improvement."

How roentgen therapy presumably improves such patients is not known. Blair suggested that benefit might result from "liberation of sulfur within the

body in such a form that it can replenish a sulfur deficiency in any part of the body." [But there is no evidence of sulfur deficiency in this disease.—Ed.]

Most writers urged that roentgen therapy not be relied on solely for treatment. Postural exercises, orthopedic measures, physical therapy, regulated rest and attention to diet should be used to supplement roentgen therapy.

3. Gold Salts. Through the years those experienced in chrysotherapy have reported disappointing results in spondylitis. Among recent reports on chrysotherapy few cases of spondylitis were mentioned; in some results were not analyzed separately. Logefeil and Hoffman gave gold in 14 cases of spondylitis of the spine ("atrophic or mixed type"). Results were as follows: "arrested" in two cases; improvement marked in two; moderate in five; slight in four; none in four. [Although treatment was given in "14 cases," results were reported for 17.—Ed.] Others were unimpressed by their results. No significant results were noted by Graham and Fletcher in eight cases, by Winkler [1945] in four. Improved was only one of seven patients treated with gold salts by Cecil, Kammerer and De Prume. "This type of arthritis appears to be refractory to gold treatment."

4. Endocrines. Because the disease affects females so rarely, certain physicians have been tempted to treat male spondylitics with female hormones. A male spondylitic, given estrogenic substance (weekly injections of theelin; total about 52,000 units in nine injections) developed swollen, painful nipples which necessitated discontinuance of treatment. Subjective improvement but no objective benefit was noted (Solomon [1670]). Presumably improved were a few patients given stilbestrol "to enhance the effect of vitamin E" (Stone), also two patients given adrenal cortical hormone (Lyon [1138]).

To "check excessive ossification by inducing decalcification" Mandl implanted into the posterior rectus sheath pieces of thyrotoxic goiter "several times" in each of four patients: two were "markedly improved" but one had a relapse after eight months.

5. Surgical Procedures. Preliminary results from vitallium cup arthroplasty of hips was "better than anticipated," but not marked: of 19 cases results were good in only 16 per cent.[139] Osteotomy of laminae and articular facets was performed by Smith-Petersen, Larson and Aufranc [1645] in six cases of spondylitis with marked spinal flexion. Distinct postural improvement resulted when the lumbar spine was operated on, but not when the thoracic region was treated.

Osteoarthritic (Hypertrophic) Spondylitis

The problem of spinal osteoarthritis is a dual one which concerns lesions of vertebral symphyses (articulations formed by two vertebral bodies and the intervening disk) and of vertebral apophyseal joints. Oppenheimer's [1324] views thereon were restated. To distinguish the two lesions Fletcher [509] suggested the names "marginal polyspondylitis" for the disease of vertebral symphyses, and "osteoarthritis of apophyseal joints" for the latter condition.

Symptoms of Cervical Osteoarthritis. Common symptoms were pain, rigidity of neck, painful shoulder, headaches, earache, sinus pains and muscular weakness of hand or arm.[970, 1230] Headaches from irritation of upper cervical roots by osteoarthritis are mainly occipital, generally chronic, recurrent and coming in sieges lasting for days (Chamberlain). In some cases the headaches occurred daily. Neckache referred to shoulders and arms sometimes occurred.

A special type of spinal osteophyte was described by Lyon [1139] who used the term "uncovertebral osteophytes" to refer to those affecting the lateral and posterolateral lips of the superior surfaces of the third to the seventh cervical bodies. These he found some distance laterally and posteriorly from the anterior longitudinal ligament. Uncovertebral osteophytes were attached to the uncinate processes, the lateral lips of the superior surfaces of the bodies of these particular vertebrae. Oblique roentgenograms were the best means for their demonstration. Most of the affected patients complained of "neuralgic symptoms of arms, neck and back of head." These consisted of boring brachial pain extending down one or both arms, tingling sensations in fingers, pain in shoulders and back of head, dizziness, headache, earache, dysphonia and transitory swelling of hand or forearm. Muscular strength was sometimes impaired, but distinct sensory symptoms were rarely noted. Treatment recommended included rest with a roll under the neck, local heat, cotton bandaging and sometimes "injections of procaine into the affected plexus."

Laboratory Data. Calcium and phosphorus metabolism was normal in two cases (Klassen and Curtis [1011]).

Treatment. The use of Sayre's extension apparatus for the treatment of cervical osteoarthritis was again described (McFarland and Krusen).

Radiant heat is first applied for 30 minutes, then massage to neck and shoulders. Traction (70 to 80 pounds [31.8 to 36.3 kg.]) is then applied slowly by means of the sling. The head is gently rotated to right and left after which traction is released slowly. This procedure is carried out twice daily for a week or more; then the patient is instructed to use the sling at home. If relief occurs, it usually begins to appear after three or four treatments.

Study of roentgenograms made during traction showed an average increase of 1.09 cm. when measured along the tips of the spinous processes, 0.65 cm. when measured along the posterior margins of the bodies, and 0.28 cm. along the anterior margins of the bodies. A tendency to straighten the normal cervical curve was noted and the diameters of the intervertebral foramina were increased. Widening of neural foramina seemed to offer a reasonable basis for the use of head traction in osteoarthritis.

"When symptoms presumably due to spinal osteoarthritis increase despite treatment, think of coincidental metastatic carcinoma." An illustrative case was reported (Buttorff [272]).

Gout and Gouty Arthritis

The recognition of "gout, the physician's shame," [1296] is important because acute gouty arthritis is, of all articular diseases, most responsive to treatment. Current writers continued to stress the matter of early diagnosis.[726, 812, 1666, 1820] Interesting reviews appeared [78] including one on "milestones in the diagnosis and treatment of gout" (Neuwirth [1295]).

Incidence. Gout was diagnosed 79 times within five years at the Cleveland City Hospital (Solomon and Stecher [1674]). Of 177 cases at the Cleveland Clinic 80 per cent were in the "executive class"; 10 per cent were physicians (Haden [726]).

Factors Governing Incidence. 1. Heredity. The presence of a hereditary factor of some cases of gout was confirmed. Among groups studied, the familial incidence was 10,[1674] 11,[214] 14 [1189] and 18 per cent.[902] Smyth and Freyberg [1619]

studied the families of two gouty persons: seven of the eight adult male members of the two families had hyperuricemia, and five had clinical gout. None of the females gave evidence of the disease. Talbott [1765] studied 136 blood relatives of 27 gouty persons. Although none "was suffering from gout or gouty arthritis" hyperuricemia (values for serum uric acid of 6.1 to 10.8; average 7.3 mg. per 100 c.c.) was present in 25 per cent. Relatives of gouty persons should be studied for the presence of unsuspected gout. According to Gibson [648] and Bauer [89] clinical gout frequently skips a generation. [No statistics given.—Ed.]

2. Sex. Of recent cases of gout 3 to 10 per cent were in females (3,[214] 5 [726] and 10 per cent [1189, 1674]).

3. Age. The age at the first acute articular attack varied between 15 and 71 (average 47.7) years in one series,[214] between 20 and 73 years in another.[1189] Fifty-one [214] and 64 per cent [1189] of patients were first affected between 40 and 60 years of age.

4. Race. Most patients were of American parentage; next often affected were those of Italian parentage.[726, 1189] Two Negro brothers had the disease.[339]

5. Dietary Habits. Of one group 40 per cent were "obese" [1189]; of Haden's [726] patients 30 per cent were 40 pounds (18.1 kg.) or more overweight; of Brøchner-Mortensen's [214] 100 patients the majority were overweight and 50 per cent drank at least five bottles of beer daily. But among aged beer-drinking pensioners Howell noted a low incidence of gout, and in India gout occurs in teetotalers and vegetarians (Sahai). Most of the 79 gouty patients of Solomon and Stecher were either on relief or their incomes were too low for them to purchase much meat. [No estimate of the diets was given.—Ed.]

[Intake of liquor and purines probably has no influence whatever on the incidence of the disease, gout, but some workers believe that such intake may be notably related to the incidence of attacks of acute gouty arthritis. Unfortunately writers failed to make this distinction or to analyze their cases from this standpoint.—Ed.]

Clinical Data. 1. General. Data on 413 new cases were reported: on 38 by Bartels, on 46 by Steinberg [1707]; on 50 by McCracken,[1189] on 79 by Solomon and Stecher and on 100 cases each by Haden [726] and by Brøchner-Mortensen. An excellent textbook chapter on gout was written by Bauer and Klemperer.[92] The clinical and diagnostic features and complications of gout and gouty arthritis were reviewed by Hench.[812]

A larval stage of gout, relatively symptomless, is present for some time before acute arthritis appears; it may be characterized by hyperuricemia, renal colic, rarely tophi (Hench [812]). In two of Talbott's cases [1764] renal colic developed from urate stones months or years before the first attack in joints.

Haden [726] considered gout "a disease of well people," but Bartel's patients would hardly agree: 14 whose disease had lasted an average of 11 years had lost an average of 20 months of work and an average salary of $3,640 with additional medical expense averaging about $500.

The big toe was first affected in 53,[725, 726] 70,[214] and 60 per cent [812] of cases. It was involved at some time in 95 per cent.[1674] An ankle was first affected in 13, the foot in 12 per cent of Haden's cases.[726] Hips were affected at some time in 2 per cent of Lockie's cases. Myositis is a common feature of gout, according to Hopkins.[862]

[We do not agree. No statistics or clinical evidence were presented in this vague paper. Gouty tendinitis occurs but acute or chronic myositis, certainly gouty and responsive to

colchicine, is rarely if ever seen in gout. Among the 400 cases of gout currently analyzed no instance of gouty myositis was found.—Ed.]

Of 100 gouty patients nine had had rheumatic fever, six of whom died of cardiac insufficiency (Brøchner-Mortensen).

2. Provocatives. Trauma, dietary indiscretions, infection and certain medications were common provocatives (Brøchner-Mortensen [214]; Hench [812]). For diagnostic purposes McEwen [1197] used high fat or high purine diets: each of five gouty persons fed a high fat diet (two weeks may be necessary) had acute attacks. High purine diets produced much greater hyperuricemia but were not more successful than high fat diets in inducing gouty attacks. But Bauer [89] could not relate acute attacks to dietary indiscretions. Changes in barometric pressure may be related to acute attacks: many prodromata accompany a fall in pressure (Talbott [1764]).

Surgical operations are prone to provoke gouty arthritis: "In cases of acute postoperative arthritis suspect gout" (Hench [812]). The value of this axiom was confirmed. Of Linton and Talbott's gouty patients subjected to 22 surgical operations postoperative arthritis developed in 86 per cent. In five cases of gout reported by Ficarra and Adams acute arthritis developed within three to five days after operation.

3. Tophi. In recent series subcutaneous tophi were present in 21,[725, 726] 28,[1189] 33,[214] and 48 per cent.[89, 812] Tophi were absent in three females [214] and in 17 males whose disease had been present 10 to 30 years.[725, 726] Osseous tophi (roentgenographic areas of erosions) were present in 25,[725, 726] 27[1674] and 31 [214] per cent.

4. Complications. Urate stones or gravel are passed by about 11 to 23 (average 13) per cent of patients at some stage of their gout, and "gouty nephritis" affects an average of 22 per cent (Hench [812]). Renal stones were passed by 11 per cent of Haden's patients,[725, 726] by "several" of Talbott's patients,[1764] by 15 per cent of Brøchner-Mortensen's 100 patients [214] but by only one of Steinberg's [1707] 46 patients. Chronic glomerulonephritis and nephrosclerosis each occurred in 7 per cent of Brøchner-Mortensen's 100 cases.[214] Systolic blood pressure was more than 150 mm. of mercury in 48 per cent of one series.[214] But only 30 per cent of Steinberg's patients [1707] had hypertension: "Gout is not an etiological factor in hypertension" nor did Steinberg [1707] believe that gout predisposes to renal irritation or angina pectoris. Gouty persons are likely to have glycosuria or "potential diabetes" according to some,[648] but not according to others.[214]

5. Unusual Clinical Data. Of 168 patients with polycythemia vera 4.8 per cent (eight) had gouty arthritis, an incidence higher than mere coincidence would allow (Tinney, Polley, Hall and Giffin); a previously reported case of gout with polycythemia and subleukemic myelosis ended fatally (Reifenstein [1447]). A case of severe gout with macrocytic anemia was noted (Sahai), also a fatal case of severe tophaceous gout with marked microcytic anemia (Lambie and Davis) and a case of severe gout with nontropical sprue (Morlock and Rosenberg). Pederson studied a case of extensive calcinosis in a male with acute recurrent gouty arthritis and hypogonadism [1356]: apparently calcinosis made its appearance at age 10 years, gouty arthritis at age 30 years. Urates were not found in the calcific deposits.

[No mention of therapy by vitamins was made in this case. Recently a few cases of gout have been seen with extensive calcium deposits in urate tophi and elsewhere resulting from improper use of concentrated vitamin D on the assumption the patients had rheumatoid arthritis.—Ed.]

Diagnosis. Criteria for diagnosis were outlined in 21 axioms by Hench.[812] Provocative tests with diets were valuable only if positive; McEwen [1197] found the high purine provocative diet was more agreeable but no more successful than a high fat diet. But Talbott [1764] considered it unnecessary to precipitate an attack

to justify a diagnosis. Of one group the diagnosis was made in the first attack in only one out of five cases (20 per cent) (McCracken [1189]). When any male suddenly develops acute monarthritis, gout should be considered even though a joint other than a big toe is affected.[725, 812]

Pathology. 1. Joints. One patient at necropsy presented extensive urate deposits in many joints, but no subcutaneous tophi were present.[1165] Urate deposits are rarely found in sacroiliac joints, joints of spine or jaw (Bauer [89]).

2. Kidneys. At necropsy kidneys of three gouty patients were studied [37, 1058, 1165]: in two of the three the kidneys contained urate deposits.

3. Other Tissues. Although urates in large tophi often surround blood vessels or nerves, they do not affect or invade them (Linton and Talbott [1108]). In four of eight cases "cirrhotic changes" affected livers at necropsy [214]; pathologic changes also affected kidneys in seven, heart in seven and aorta in eight cases. In the case of Lambie and Davis [1058] lesions of bone marrow, kidney and heart were of special interest. [Were the specimens preserved in a formalin-containing fixative, rather than absolute alcohol? If so, the local cardiac intraventricular lesion may have represented a rare intracardiac tophus spoiled in preparation.—Ed.]

Laboratory Data. 1. Blood Uric Acid. Talbott [1764] again insisted that practically every gouty patient presents hyperuricemia, but others disagreed. Fifteen to 20 per cent of gouty patients were found by others to have normal uric acid concentrations in blood or serum. Thus the serum uric acid was increased in 80 per cent of 95 patients [214]; blood urates were increased in 86 per cent of Haden's cases [725]; blood levels of uric acid were below 5 mg. per 100 c.c. in 18 per cent of McCracken's 50 cases.[1189] According to Hench [812] 75 per cent will have hyperuricemia at some stage of gout.

Patients often take large doses of aspirin shortly before blood uric acid studies are done; this markedly decreases the concentration in the blood. Patients should avoid urate eliminants for 48 hours before blood tests (Lockie; Talbott [1764]). Gouty patients without renal insufficiency clear urates normally and may excrete large amounts of urates (Talbott [1764]).

To determine uric acid the method of Folin or Benedict was recommended. Neither test offers undue technical difficulties but only great care in preparing reagents and frequently checking controls assures reliable results (Bauer [89]).

2. Sedimentation Rates of Erythrocytes. Rates were increased, often markedly, during attacks, but returned to normal generally soon, sometimes tardily thereafter.[214, 725, 726, 728, 1115, 1189]

3. Miscellaneous Tests. Data on liver function tests, blood counts and other laboratory tests were reported by Brøchner-Mortensen.[214] Various tests for abnormal colloidal states in blood were applied by Milles and Salt [1244]: formol-gel test, Weltmann reaction, Takata-Ara reaction. No changes were specific for, or characteristic of, gout.

Etiology. Opinions on etiology were summarized.[812] Gout was considered a manifestation of deranged purine metabolism,[1674] a condition related to increased formation of uric acid [1764] or to abnormal deposition of urates.[648] Lead poisoning was not a factor in 100 cases.[214]

[No new data of significance were presented. The cause remains unknown.—Ed.]

The causes of acute gouty arthritis may be quite different from the cause of gout. Postoperative gouty arthritis was considered by Tuohy to result possibly

from postoperative ketosis incident to a low dietary intake.[1820] But in five such cases Ficarra and Adams [555] noted hypoproteinemia (4.5 to 5 mg. per 100 c.c. of plasma). The hypoproteinemia (from a low postoperative intake of protein) was thought to stimulate endogenous purine metabolism, resulting in "hyperuricemia which is the precipitating agent for the formation of tophi or an osteoarthritic gout."

[It has not been proved that acute attacks result from, or are associated with, urate deposition in joints, nor that hyperuricemia bears any consistent or causal relation to acute attacks.—Ed.]

Treatment. Usual principles were restated.[89, 812, 1764] No new successful remedies were described. Gout itself is incurable; patients will have the disease through life.[1765] But much can be done to control the frequency and severity of acute attacks.[79, 812, 1666] Hereditary candidates and hyperuricemic relatives of patients with active gout should live moderately and avoid obesity and the various provocatives of acute gouty arthritis.[812, 1765]

1. Treatment of Attacks. Colchicine should be given until pain is relieved or gastrointestinal symptoms occur.[93, 812] Patients who recognize prodromata of an attack may abort attacks by prompt use of colchicine. "It is better to take a few tablets of colchicine for a false alarm than to permit an attack to become established" (Hench [812]). Calomel and a saline aperient were prescribed by Ball. Absolute rest in bed is usually indicated; premature resumption of normal activity may precipitate a flare-up. The use of physical therapy after attacks "to absorb exudation and prevent residual fibrosis" was recommended by Solomon and Stecher. [Physical therapy, except for the use of hot or cold compresses, is generally unnecessary. More strenuous measures (baths, massage) may provoke an exacerbation, a "cure-crisis."—Ed.]

2. Interval Treatment. Most writers favored the use of interval therapy. Some who have formerly discounted its value now at least recommend the prophylactic use of colchicine. The usual interval treatment included diets low in purine and fat, high in carbohydrates and the periodic use of salicylates or cinchophen.[79, 303, 812, 1296] Restriction of purines presumably relieves the already overburdened metabolizing mechanism, and may at least lessen the amounts of urates available for ectopic deposition. A low fat intake prevents retention of purine, a high carbohydrate intake favors elimination of endogenous urates. A variety of detailed menus offers welcome aid to the gouty.[636] Some physicians prohibited the use of alcohol [79, 812]; others suggested that it be regulated by rules of temperance rather than abstinence.[1765]

Although many now prefer salicylates as a urate diuretic,[812] Bartels administered cinchophen three days a week; as treatment progressed he made periodic estimations of the concentration of serum uric acid; when it was reduced cinchophen was given only twice or once a week and when it approached normal, cinchophen was not given. According to Bauer [93] large doses of salicylates need not be given continuously except to patients with rapidly recurring gouty arthritis. The site of action of cinchophen and salicylates is probably the renal tubules: the drugs inhibit resorption of urates. To increase the solubility of urates alkaline powders were used.[812, 1765]

A patient given 17 c.c. of pure sterile uricase within four days experienced no untoward local or general reaction but also no reduction of articular pain or swelling and no lowering of plasma uric acid (Oppenheimer and Kunkel). The dosage was probably "far too small."

Colchicine as a prophylactic has through the years been considered useless. But some are now reviving its use. Talbott's plan [1765] follows: for patients who have only one attack each year, "a few colchicine tablets" (each gr. 1/120 [0.00053 gm.]) only

when mild articular aches and pains appear. [Patients do not refer to such minor episodes as "attacks" and do not include them when asked about attacks.—Ed.] Talbott recommended for others who have only one attack a year one or more tablets a day to one or two a week; for those with more than two attacks yearly, two or three tablets daily for two to three days a week; for patients with severe gout, one to three tablets daily continuously. Several patients followed this last schedule for as long as five years with no intolerance or untoward effect. [One of us, L.M.L., recently saw a patient who had taken colchicine, 1/120 grain (0.00053 gm.) three times a day for five years with no reaction. It had been prescribed by a psychiatrist; the patient thought it was a sedative.—Ed.] Tolerance to the drug did not occur and if an acute attack occurred full doses of colchicine were effective. According to Talbott [1765] such intermittent use of colchicine may abort mild attacks, convert severe attacks into mild ones, keep the patient "colchicine-conscious" and alerted to use it promptly when an attack occurs.

[From this it would appear that colchicine in his hands has not prevented all attacks. Nevertheless continued studies are in order.—Ed.]

Three regimens to prevent postoperative gouty arthritis were reported. Hench [812] used a purine-free diet and salicylates or cinchophen five days before and five days after operation. Linton and Talbott [1108, 1765] recommended the use of colchicine, three tablets daily (each $\frac{1}{120}$ grain) for two or three days before and after operation. Thus the incidence of postoperative arthritis was reduced from 86 to 8 [1765] or 10 per cent.[1108] Ficarra and Adams [555] recommended the prevention or correction of postoperative hypoproteinemia. [No details given.—Ed.]

3. Tophectomy. Large tophi should be removed to prevent or correct ulceration.[812, 1108] When débridement is done thoroughly, prompt healing occurs. The surgical treatment in 11 such cases was described by Linton and Talbott [1108] with fine colored illustrations.

4. Results of Treatment. An "interval régime" provided to Bartels' patients "indisputable benefit." On this plan only seven minor attacks of acute gouty arthritis occurred in 31 patients as compared with 84 major attacks during a comparable period before treatment. Even patients with chronic gouty arthritis were benefited. Despite instructions, patients often fail to control their gout, not so much because of the limitations of treatment as for other reasons listed by Hench.[812]

Mortality from Gout. Between 1930 and 1939 deaths attributed to gout numbered 2,400 in England and Wales, only 25 in the United States. Possible reasons for this "remarkable contrast" were discussed (Bowerman).

Studies on Colchicine

Three patients with severe inoperable carcinoma were given rather large doses of colchicine (13 mg. in four days, 29 mg. in seven days, 28 mg. in 64 days; 0.5 mg. = $\frac{1}{120}$ grain). Colchicine poisoning with granulocytopenia developed in the first two. The effect of the colchicine on normal and cancerous tissues was studied at necropsy by Brown and Seed who considered colchicine a dangerous drug capable of producing severe depression of bone marrow. In one case peripheral neuritis of the popliteal nerve was probably caused by the colchicine. The drug exerts a toxic effect on living cells which commonly arrests mitosis at an early stage, usually the metaphase; it may lead to cell death. The

effect of colchicine is general; it is selective only in the sense that the drug first affects tissues which have the highest metabolism and rates of cell division: bone marrow, skin, lymphoid structures, tumors. Colchicine produces no specific morphologic changes. Other histopharmacologic studies on colchicine were made (McPhail and Wilbur [1210, 1211]).

[The doses used in the first two cases were perhaps larger than those generally used in acute gouty arthritis. But those who prescribe more or less continuous doses of colchicine for prophylactic purposes should be on the lookout for toxicity: granulocytopenia or neuritis.—Ed.]

Cinchophen Toxicity

The Council on Pharmacy and Chemistry [394] published a report on "The Present Status of Cinchophen and Neocinchophen" with a review of toxic reactions, contraindications and indications. Between 1925 and 1936 were reported about 191 cases of toxic hepatitis with about 88 deaths attributed to cinchophen products: a yearly average of about 16 cases of toxic hepatitis including about seven deaths. The probable fatality rate was one death in 10,000,000 ± doses. A questionnaire [393, 394] sent to 266 professors of medicine, pharmacology and pathology revealed that only 14 per cent considered these drugs indispensable; a minority (24 per cent) stated that they had therapeutic effects not accomplished more safely otherwise; only 13 per cent gave them with confidence of safety and only 11 per cent considered that cinchophen toxicity could be satisfactorily counteracted. But 24 replies considered these drugs "particularly useful in the treatment of gout." The Council concluded: "The drug should not be employed unless the attending physician feels that the patient's need for it fully justifies the risk, possibly for the relief of pain in certain cases of so-called rheumatism, including gout, and some types of arthritis when safer substitutes fail to afford relief." But others concluded the fear of cinchophen has been exaggerated.[496, 726, 812, 1435, 1436, 1437] A review of toxic reactions, and experiences with gout suggests that certain patients, especially rheumatoids, may be somewhat more susceptible to cinchophen toxicity and that gouty patients may be relatively safe. Certainly the majority of cases of toxicity have been in cases of rheumatoid arthritis and very few indeed in the gouty.

Two deaths presumably related to cinchophen were reported. A woman, aged 56 years, presumably with rheumatoid arthritis of six weeks' duration was twice given typhoid vaccine intravenously (Yott) (first dose 10,000,000, second dose, 25,000,000 bacilli). Three days after the second reaction icterus appeared, later coma and death in three weeks from acute yellow atrophy. Unknown to the physician the patient had taken on a pharmacist's advice "small doses of cinchophen" for six weeks.

A woman, aged 38 years, who had had jaundice of unknown type six years before, developed rheumatoid arthritis for which she took oxyliodide (containing cinchophen), duration and amount unknown (Mass [1164]). During the next five years she had recurring jaundice from which she recovered. She died of a perforated gastric ulcer. At necropsy toxic hepatic cirrhosis, presumably related at least in part to the cinchophen, was found.

[In both these cases the rheumatoid arthritis subsided during jaundice.—Ed.]

Among 100 arthritics given cinphophen daily for more than a year no liver damage was found.[496] Among Rawl's [1435, 1436, 1437] 500 patients who had taken cinchophen "over a period of years" no granulocytopenia occurred, but a variety of nonfatal reactions were noted including jaundice in two cases. The use of natural vitamin K seemed to lessen the toxic effects of cinchophen but agranulocytosis developed in one patient given cinchophen and *synthetic* vitamin K. Synthetic vitamin K contains the quinone radical which may produce agranulocytosis.

The production and prevention in animals of gastric ulcers from cinchophen, and the effect of cinchophen on certain liver functions were studied.[31, 32, 132, 1632, 1633]

[In our previous eight Reviews (1932–1940) [1] we reported 16 cases of cinchophen poisoning: nonfatal agranulocytosis in two cases, hepatitis in 14 (fatal in nine, nonfatal in five). The drug had been taken as follows: for rheumatoid arthritis in two cases; "chronic polyarthritis" in one; "rheumatic fever" in two; sacroiliac pain in one; pains in chest and shoulder in one; gonorrheal arthritis in one; "rheumatism" in one; osteoarthritis in one; cholecystitis in one; "colds" in two; for unstated reasons in three. No definite case of gout was included unless Kersley's (1937) case [16] of transitory nonfatal jaundice from one dose given for an unstated disease was in a patient with gout. We must conclude, therefore, that in cases of gout cinchophen toxicity has rarely been reported. Even so we recommend a trial of salicylates before resorting to cinchophen. Only in cases of gout not otherwise controlled, does the use of cinchophen seem justified. In particular we avoid its use in rheumatoid arthritis.—Ed.]

Uric Acid Problem

Methods. 1. Blood. The uric acid partition in gout and in hepatic disease was studied by Adlersberg, Grishman and Sobotka. The uric acid partition (the relation of free to bound, nonultrafiltrable uric acid) of normal blood serum is comparatively constant, the bound uric acid comprising 4 to 24 (average 16) per cent of the total serum uric acid. In many diseases this ratio remains normal but in gout and in hepatic disease the free uric acid diminishes, the bound (and the total) uric acid content increases. Gout may be accompanied by signs of hepatic damage; to what extent hepatic dysfunction is related to gout is not known. In 10 gouty patients the bound uric acid content of serum varied from 1 to 65 per cent of the total uric acid content. Gout with marked hyperuricemia may be associated with a normal uric acid partition; but gouty patients with a normal total uric acid content may demonstrate a high bound uric acid ratio. Such findings may have diagnostic and therapeutic significance.

[This interesting work should be studied further.—Ed.]

Other new methods were discussed.[223, 251] The direct method of Benedict was most suitable for determining uric acid with a photoelectric colorimeter.[1269] Using a new method for preparing phosphotungstic acid, uric acid clearances of human blood were found to average about 15 c.c. per minute, about half that previously reported.[179]

2. Urine. Discrepancies in various methods for determining urinary uric acid were discussed.[1106] Based on the action of uricase a method to measure urinary uric acid in the presence of methylated uric acid was developed. This "uricase method" showed that caffeine or theophylline do not increase excretion of "true uric acid" (Buchanan, Block and Christman [234, 235]).

Physiology. 1. Human Beings. The uric acid content of blood is normal during normal pregnancy, may be increased in toxemias of pregnancy especially just before eclamptic convulsions presumably due to a reduction in glomerular filtration.[405, 566, 1546]

In pernicious anemia the uric acid content of blood increases when the normoblasts in bone marrow diminish and when reticulocytes in blood increase.[1692]

The excretion of uric acid was notably increased by intravenous injections of diodrast but not by hypertonic solutions of glucose, 50 c.c. of 50 per cent glucose (Bonsnes, Dill and Dana). In man there is only a general parallelism, not a specific relationship, between the clearance of uric acid and urea: "it is improbable that the rise in incidence in gout which occurs with aging is primarily due to a progressive and selective impairment of the renal ability to secrete uric acid associated with renal and vascular senescence" (Stieglitz). The metabolism of lactic acid (and the blood levels of lactate and pyruvate) seems to influence uric acid excretion (Michael).

2. Animal. Injections of uricase into hens lowered the blood uric acid; the effect of a single injection lasted eight to 24 hours (Oppenheimer and Kunkel [1325, 1326]). Renin, injected into dogs, increased the uric acid content of blood and urine.[1547] Alloxan and dialuric acid, a reduction product of alloxan, injected into pigeons (a single dose of 60 to 125 mg. per kilogram of body weight, less than half the diabetogenic dose) sometimes caused marked increases in blood uric acid and deposits of sodium urates in all serous membranes (pericardium, pleura, surface and parenchyma of liver, kidneys).[670]

CASE REPORTS

WEBER-CHRISTIAN'S DISEASE: REPORT OF A CASE *

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WEBER-CHRISTIAN'S disease, or relapsing febrile nodular, non-suppurative panniculitis, is a disease of unknown cause, characterized by the appearance of crops of inflammatory and necrotic subcutaneous nodules chiefly on the arms, legs, and trunk and by a definite constitutional reaction. The disease commonly affects young women and generally results in recovery, but runs a protracted course, which may last from one month to 15 years. There are no characteristic laboratory findings. The nodules may regress with fibrosis and atrophy at the original site. A recent review of the literature [1] reveals 28 recorded cases of Weber-Christian's disease, and more recently, a few additional cases have been described.[2, 3] Another case of this disease, proved by biopsy, and possessing several noteworthy features, is reported here.

CASE REPORT

H. B., a 33 year old, single, white woman, was admitted to the Edward J. Meyer Memorial Hospital, October 30, 1944, complaining of nodules of the skin, weakness, chills and fever. During her hospital stay there appeared new crops of subcutaneous nodules accompanied by exacerbation of symptoms. Treatment was supportive only, and the patient was discharged December 29, 1944, free of symptoms and subcutaneous nodules.

History: On entry to the Edward J. Meyer Memorial Hospital the patient stated that subcutaneous nodules had appeared on the arms in August 1944. Later, nodules were noticed on the legs, buttocks and breast. The nodules began as discrete lesions which increased in size and became tender. They occurred in crops, each new outbreak being accompanied by malaise, chills and fever.

In 1942, the patient had a cholecystotomy for "cholelithiasis," following which an incisional hernia developed. From January 1943, to October 1944, there followed five admissions to another hospital for complaints of abdominal cramps, nausea and emesis, loss of weight, chills and fever. The patient's leukocyte count ranged from 15,000 to 26,000 cells per cu. mm. with 84 per cent polymorphonuclear leukocytes. The abdominal symptoms were explained on "subacute intestinal obstruction" for which surgical repair of the incisional hernia was attempted. The diagnosis of the cause of the constitutional symptoms, however, remained obscure; septicemia and generalized vascular disease were considered among the possibilities. Treatment during the five admissions included the administration of sulfathiazole, sulfadiazine, sulfamerazine and penicillin.

History was also obtained that the patient had suffered one "grand mal" convulsion and two "petit mal" seizures in May 1944, following which dilantin was prescribed. There was a family history of bronchial asthma. The patient complained

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of loss of weight of 67 pounds in the past two years, which she attributed to an inadequate diet.

Physical Examination: The patient was a pale, obese, white woman of sandy complexion, moderately ill. Temperature, 99.4; pulse, 118; respirations, 20; and blood pressure, 140 mm. Hg systolic and 100 mm. diastolic. Many fine râles were heard in the base of the left lung. The heart was not enlarged. There was a soft systolic murmur over the precordium. The abdomen showed a grapefruit sized reducible incisional hernia in the right upper quadrant.

In the subcutaneous tissue of the arms, legs, buttocks, abdomen, right breast, posterior chest and fingers were scattered discrete tender nodules ranging in size from 1.0 to 2.5 cm. in diameter, some of which were in short chains. The largest were found in the legs, and occasionally were fluctuant. The skin overlying the nodules was warm and red.

Laboratory Data: The urine was negative. Hemoglobin: 10 grams. Red blood cell count 3,620,000. White blood cell count 17,500 with 10 per cent bands, 61 per cent filaments, 25 per cent lymphocytes, 3 per cent basophiles, 1 per cent eosinophiles. Thirteen blood cultures were negative. The Wassermann test and agglutination reactions for undulant fever were negative. Chemical examination of the blood disclosed: Glucose 90 mg. per cent; cholesterol 86 mg. per cent; calcium 9.8 mg. per cent; and total proteins 7.2 gm. per 100 c.c. The tuberculin test was 2 plus after 48 hours.

The electrocardiogram showed sinus tachycardia with no axis deviation.

On roentgen-ray examination, the heart was full sized. The left lung showed some congestion at the base, which cleared on subsequent films. The skull and long bones were normal.

Biopsy: Biopsies were made of early lesions as they developed and from a late lesion which had been present before the patient's entry to the hospital. In an early lesion the deep parts of the subcutaneous fat tissue showed edema and hyperemia in the septa. Leukocytosis of the capillaries and hemorrhage were present. There was perivascular infiltration of neutrophiles and round cells; the latter type of cell predominated. Vascular lumens were patent. The corium revealed only minimal perivascular infiltration. In a moderately advanced lesion, regressive changes were noted in fat cells. There were focal areas of brown pigmentation. The oldest lesion represented a distinct, active, chronic inflammatory and regressive process of nonspecific character. The septa were edematous and infiltrated with neutrophiles, round cells and eosinophiles. Large macrophages, some with foamy cytoplasm, and multinucleated giant cells were seen particularly in the neighborhood of a large fat or oil cyst with granulation in the wall and with necrotic material in its center. Small cysts, sometimes with crystalline material as content, had also formed. In relation to the large cyst lay a focal calcified particle. The endothelial cells of vessels were swollen. There was inflammation in the walls of vessels and perivascular tissue. Regressive changes involved vascular walls. Biopsy of the gastrocnemius muscle disclosed no inflammatory or regressive changes in vessels. Smears and cultures from cloudy, yellow fluid of the large cyst proved negative for bacteria.

Course: During the first 13 days of the patient's hospitalization, the temperature rose to 102.4°, the pulse rate to 120 per minute, and crops of nodules appeared. One nodule developed on the dorsum of the left hand at the site of venipuncture. The temperature and pulse rate leveled off gradually as new nodules appeared less frequently. Biopsy sites showed poor healing. The patient was discharged on the fifty-ninth hospital day with no symptoms and a normal temperature. Treatment had been symptomatic. Three whole blood transfusions had been given on empirical grounds.

Four months after discharge, no nodules were present, and no atrophy was noted

at site of previous nodules on the hand, arms, and legs. The patient complained only of recurrent convulsions, which occurred at intervals of three or four weeks, and for which she had just resumed dilantin therapy.

In June 1945, six months after discharge, the patient suffered a relapse of her disease, necessitating 16 weeks of hospitalization at another institution. This relapse occurred though the only treatment, in the interim, had consisted of dilantin in effective therapeutic doses. Manifestations were identical with those of the first attack, with the difference that the constitutional reaction was more severe, remission longer delayed, and the distribution of nodules more extensive. Many nodules appeared in the breasts and several on the hands. On two separate occasions during this relapse, a site of previous biopsy broke down and drained spontaneously for a day or two. Treatment, again, was symptomatic.

Seen again, one year after discharge from the Edward J. Meyer Memorial Hospital, the patient offered no complaints, being free now of even gastrointestinal symptoms. A successful herniorrhaphy had been performed during the second hospital admission. The surgery had been tolerated well, with the exception that a small crop of nodules appeared in the immediate postoperative period, only to disappear rapidly.

Examination failed to reveal atrophy of the subcutaneous tissue where nodules had been noted previously.

Discussion

From the clinical and biopsy findings, this case fulfills the fundamental requisites of Weber-Christian's disease. The patient was a 33 year old woman whose outstanding complaints were numerous tender, subcutaneous nodules which appeared in crops, and which were accompanied by malaise, fever, and increased pulse rate. It was felt that these symptoms had existed for two years. Other symptoms including convulsions (history), nausea and emesis, and abdominal cramps were best explained on the basis of epilepsy, incisional hernia, and hypertensive vascular disease. Biopsy of clinically typical nodules showed them to be of an inflammatory-regressive character.

Noteworthy features of this case include: (*a*) atypical distribution of lesions, (*b*) marked leukocytosis, (*c*) unusual biopsy findings. A nodule was present in the right breast, where involvement has been rarely encountered. Although a recent review of the literature states in regard to the reported distribution of lesions that only the hands have been spared, clinically typical nodules were observed on the dorsum and finger of the hand of our patient. In evaluating this observation we must admit that the nodule on the dorsum developed following venipuncture.

Our patient ran a persistent polymorphonuclear leukocytosis; only four out of 28 cases compiled by Larkin showed an increase in the white count.

By multiple biopsies of nodules it was possible to study the subcutaneous lesion from early to late phases, and its relation to the overlying skin. Focal calcification was noted in an advanced lesion; this has rarely been seen. An advanced lesion also showed pseudocysts containing fluid, which was proved to be sterile pseudo-pus. While it is felt that liquefaction in nodules represents an unusual manifestation in Weber-Christian's disease, Shaefer [4] interpreted the break-down, rupture and discharge of lesions of sufficient differential significance to place his case under the label of "liquefying nodular panniculitis." Perhaps it was this factor which led to the poor healing noted in our case at the biopsy

site; and because of the poor healing, elective repair of an incisional hernia was deferred until the second hospital admission.

The cause of Weber-Christian's disease is unknown. Many cases give a history of iodide or bromide ingestion and etiologic significance has been attached to such a history. Our patient was never administered iodides or bromides; however, there was the history of prolonged treatment with many different sulfonamide preparations; the question is raised as to the possible etiologic significance of such therapy.

SUMMARY

A case of Weber-Christian's disease in a 33 year old white woman is reported. Noteworthy features of this case were the presence of nodules on the hand and in the breast, a leukocytosis of 17,500, and focal calcification in biopsies of subcutaneous nodules. There was a history of ingestion of many different sulfonamide preparations. The question is raised as to the possible relation between prolonged administration of sulfonamides and the occurrence of Weber-Christian's disease.

We are indebted to Dr. Samuel Sanes for the description of the biopsy findings.

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PULMONARY EMBOLISM *

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IT has long been recognized that thrombi originating in the right side of the heart constitute a frequent threat of pulmonary embolism.

Many generations of medical students have been taught that sudden tragic deaths from massive pulmonary embolism following laparotomy, or occurring post-partum, resulted from thrombosis of the pelvic veins. An appreciable mortality which varied little in major clinics was thought to be inevitable and unavoidable.

In the past three years, it has been demonstrated beyond reasonable doubt that thrombosis of the deep veins of the legs is the usual cause of postoperative pulmonary embolism.

Thrombophlebitis complicating certain acute infections, particularly typhoid fever and pneumonia, is thought to be a less frequent cause.

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There still remains another group of cases in which thrombi develop in the systemic veins, in the absence of all known etiologic causes for their formation. When pulmonary embolism develops under these circumstances, it is extremely likely to remain unrecognized, especially if its symptoms and signs are attributed to some other acute pulmonary disease.

Emboli which reach the lungs originate principally as thrombi which are formed either in the right side of the heart or in the systemic veins. Thrombi of cardiac origin may develop in the auricular appendage and be swept from there into the pulmonary artery and into the lungs. Pulmonary embolism may also result from dislodgement of a thrombus formed in the right ventricle at the site of myocardial infarction. Occasionally, acute or subacute bacterial endocarditis may be present on the right side of the heart, and the development of multiple thrombi on either the tricuspid or pulmonary valve, or both, may produce showers of pulmonary emboli.

Five years ago, a patient with subacute bacterial endocarditis with overwhelming invasion of the blood stream by *Streptococcus viridans,* was seen by the author. Almost all of the valvular vegetations were confined to the tricuspid

FIG. 1. M. M., female, age 50 years. Subacute bacterial endocarditis, with *Streptococcus viridans* septicemia. Note vegetations on tricuspid valve.

valve, and the rapidly fatal clinical course of this disease was characterized by repeated episodes of pulmonary infarction. Figure 1 illustrates the vegetations on the tricuspid valve, and figure 2 the multiple infarcts in both lower lobes of the lung, which resulted from detachment of thrombi from the tricuspid valve leaflets.

FIG. 2. (Same patient as figure 1.) Note multiple infarcts in both lower lobes of the lung.

A more important form of pulmonary embolism, especially from the standpoint of diagnosis, prophylaxis and treatment, is that type which results from thrombosis in the femoral veins.

The medical profession is deeply indebted to Allen and his associates [1, 2, 3] who, over the past three years, have emphasized the frequency with which femoral thrombosis occurs postoperatively. They have shown how a simple surgical procedure has been able to reduce significantly the morbidity and mortality from that type of pulmonary embolism which results from thrombosis of the deep veins of the legs.

"Contrary to the previously held belief that almost all instances of sudden postoperative death from pulmonary embolism resulted from a massive thrombus

formed in the pelvic veins, it is now thought that the great majority of these emboli have their origin in thrombosis of the deep veins of the lower extremities. In support of this opinion, Castleman [4] states that 95 per cent of all emboli exclusive of heart origin can be traced to the leg veins." [5]

Allen accords to Homans the credit for first suggesting that it was feasible to ligate the deep leg veins to prevent pulmonary infarction and embolism.

In 1943 Allen, Linton and Donaldson [1] reported interruption of the femoral vein or veins in 202 patients operated on between 1937 and 1943. Seventy-eight patients had bilateral ligation. There were no deaths and no disabling sequelae in this group.

Allen's most recent contributions [2, 3] present his statistics up to October 1, 1945. He and his associates have performed a total of 1468 femoral vein ligations on 816 patients.

Between 1937 and 1942, bilateral interruption of the femoral veins was performed on 39 per cent of patients operated upon. In 1943 bilateral operations were done in 81 per cent; in 1944, 97.9 per cent, and in 1945 (up to October 1), 98.2 per cent. These statistics are entirely in accord with the expressed opinion of these authors that bilateral operation is desirable even in the absence of clinical evidences of bilateral thrombosis.

In the entire group of 816 patients, the indications for operation were as follows: Leg signs as first symptom, 47 per cent; chest pain as first symptom, 34.4 per cent. No prophylactic interruptions of the femoral veins were done between 1937 and 1942. In 1943, prophylactic ligations comprised 9.2 per cent of those operated upon; in 1944, 25.7 per cent, and in the first nine months of 1945, 36.7 per cent.

It is apparent from these figures that these authors are now convinced of the value of femoral vein interruption in the prevention of pulmonary thrombosis and embolism. Allen [3] now advises prophylactic femoral vein interruptions on all patients over 65 years of age prior to operative procedures which prevent early rising.

No fatalities have resulted from 1468 venous interruptions, and there has been only one death from massive embolism following femoral vein ligation. The embolus in this case came from the profunda femoris vein eight days after the superficial femoral had been ligated.

Hamman [6] states that venous thrombosis is usually unsuspected until pulmonary embolism occurs, and that the signs of femoral thrombosis may appear only after pulmonary embolism has taken place. The pulmonary infarcts are usually multiple and peripheral, and are frequently productive of sterile pleural effusion. When the thrombi are infected, multiple lung abscesses and empyema usually result. The symptoms depend on the size of the vessel occluded. Unless the patient succumbs rapidly to shock from massive embolisms of the pulmonary artery, the usual symptoms are severe pain in the chest, tachycardia, dyspnea, cough, and bloody sputum. The physical signs are fever, râles or frictions, or both, usually over one or both lower lobes, followed shortly by physical signs of consolidation and moderate pleural effusion.

Hamman's observations are almost prophetic when they are compared to the clinical picture of the patient who instigated this report.

Allen and his associates [1, 2] divide femoral thrombosis into two groups,

phlebothrombosis and thrombophlebitis. Phlebothrombosis is a term used by Ochsner and DeBakey [7] to designate a non-inflammatory lesion. Homans [8] prefers the term bland thrombosis for the same condition. This type is insidious, in that it may produce no symptoms until pulmonary embolism occurs. It is particularly dangerous because the thrombus, not being tightly adherent to the veins, is easily dislodged. The term thrombophlebitis is used to designate the usual *phlegmasia alba dolens,* which in its fully developed state is characterized by pain and swelling of the affected limb with signs of systemic infection. Embolism is much less likely to occur in these cases, because the thrombus is more likely to be adherent within the inflamed vein.

This brief survey of the etiology of pulmonary embolism, its clinical recognition, and its prophylaxis and treatment, is presented as an introduction to the following case report:

H. L., a white male, age 37 years, was seen in consultation with Dr. Joseph Freeman on May 30, 1945, and admitted immediately to the Hospital of the University of Pennsylvania. His illness began one week previously with fever and pain in the left side of the chest, followed three days later by repeated episodes of frank hemoptysis. On admission, physical examination revealed partial consolidation of both lower lobes, with frictions over the left base. The leukocyte count was 22,400, with 86 per cent of neutrophiles. Examination of the sputum revealed no tubercle bacilli on smear, and no pneumococci on culture. Hemolytic streptococci, alpha prime streptococci and *Streptococcus viridans* were present in each of two sputum cultures, on June 4 and 9, respectively.

Roentgen examination of the chest by Dr. E. P. Pendergrass on the day following admission showed bilateral basal consolidation with a small effusion at the left base. It was our opinion that this patient had bronchopneumonia, and he was given sulfadiazine in full doses for six days, with no effect. He was then given 20,000 units of penicillin intramuscularly every three hours for the following 14 days, with no obvious change in his clinical course. On June 12, 550 c.c. of sterile serous fluid were removed from the right chest.

A second roentgen examination by Dr. Robert Barden three weeks after admission still showed bilateral patchy basal consolidation, and an old lesion, presumably tuberculous, at the extreme left apex.

On June 12, the patient suddenly went into profound shock, with marked dyspnea, pallor, and sweating. In view of a dubious previous history of peptic ulcer, hemorrhage from the gastrointestinal tract was suspected, but there was no hematemesis and no melena. He recovered from shock in a few hours. On June 16 the patient complained of slight discomfort in the left calf. Nothing abnormal was found on examination. He was not tested to determine if pain in the calf occurred on dorsiflexion of the foot. When this test is positive, it may, according to Homans, be indicative of thrombosis in the deep veins of the leg. He was discharged from the hospital on July 1, on the sixth afebrile day.

On July 6, coincident with a slight elevation of temperature, he complained of pain in his right chest. Examination on July 23 revealed no abnormal physical signs. At this time the patient had regained eight of the 20 pounds lost during his month's sojourn in the hospital.

During the first week in August there was a recurrence of fever with pain in both sides of the chest. Examination revealed frictions and bilateral patchy consolidation. The fever and pain persisted for 12 days. Roentgen examination by Dr. Barden on August 15 showed a small pleural collection at the left base, with exaggerated lung markings at the site of the previous pneumonic lesions. The lymph nodes in the left hilum were thought to be enlarged.

On November 15, he again developed fever, pain in the right side of the chest, and dyspnea. On November 27 he had repeated bouts of hemoptysis. He was readmitted to the hospital on December 1, 1945, with signs of partial consolidation of both lower lobes, and a small pleural effusion on the right side. Roentgen-ray examination by Dr. Philip Hodes revealed a bronchopneumonic process in the right lower lobe with moderate effusion in the right chest, and a little fluid in the left. Right thoracentesis yielded 280 c.c. of sterile blood-tinged fluid. The laboratory studies were essentially the same as those of the first admission.

On December 11 the patient complained of mild discomfort in the left thigh. His temperature was normal at this time. Examination revealed tenderness and induration over the left saphenous vein. It was not until this time that it was realized that this patient was probably having repeated episodes of pulmonary embolism from thrombosis of the left femoral vein. Surgical consultation with Dr. E. L. Eliason was requested, and he concurred in this opinion. The patient was operated upon by him on December 17, 1945. Because of the operative findings and the extensive surgical procedure which was required, the operative notes by Dr. Robert Welty are quoted verbatim:

"A longitudinal incision was made over the region of the saphenofemoral junction. The saphenous vein was exposed. It was completely occluded by thrombosis and in addition many of its tributaries also were occluded in a similar fashion. The thrombosis extended to involve the femoral vein also. By dissecting upward beneath Poupart's ligament it could be demonstrated that the thrombosis persisted, therefore the incision was extended above Poupart's ligament and by dividing the external oblique it was possible to identify the external iliac at this point. The thrombosis continued to extend so a muscle splitting incision was made dividing the internal oblique and transversalis and reflecting the peritoneum and preperitoneal fat medially. In this way dissection could be carried even farther, but finally a higher muscle splitting incision was necessary in order eventually to identify the most proximal portion of the thrombosis. This was present at the confluence of the external and internal iliac vein. The internal iliac vein was not thrombosed. The external iliac vein was thrombosed up to the point of the confluence and the common iliac was ligated just proximal to this point. The common iliac vein above this point was normal in size and showed no evidence of disease. Prior to ligation it was opened and a retrograde flow of blood was readily obtained with no evidence of a free lying thrombus in this portion of the vein.

"The segment of external iliac and femoral vein was then dissected free down to the point of entrance of the deep femoral vein and this segment was excised. The tributaries were ligated, a single Penrose drain was placed down in the bed from which the vein had been removed and the muscle was closed in layers by interrupted sutures of catgut, the skin being approximated by interrupted vertical mattress sutures of fine steel wire."

Although the operation required almost four hours, the patient's convalescence was entirely uneventful and he was discharged on December 30, 1945, the thirteenth postoperative day.

He had had at least four episodes of pulmonary embolism between April 23 and November 15, 1945. Since operation five months ago, he has remained free of symptoms and in normal health, except for slight residual edema of the left leg, which is not incapacitating him in any way.

Figure 5 is a photograph of the common femoral vein removed at operation, opened to show the extent and magnitude of the thrombus. When the vein was opened it was solidly and completely occluded by thrombus, most of which was not adherent to the inside of the vein. Had this thrombus dislodged in one

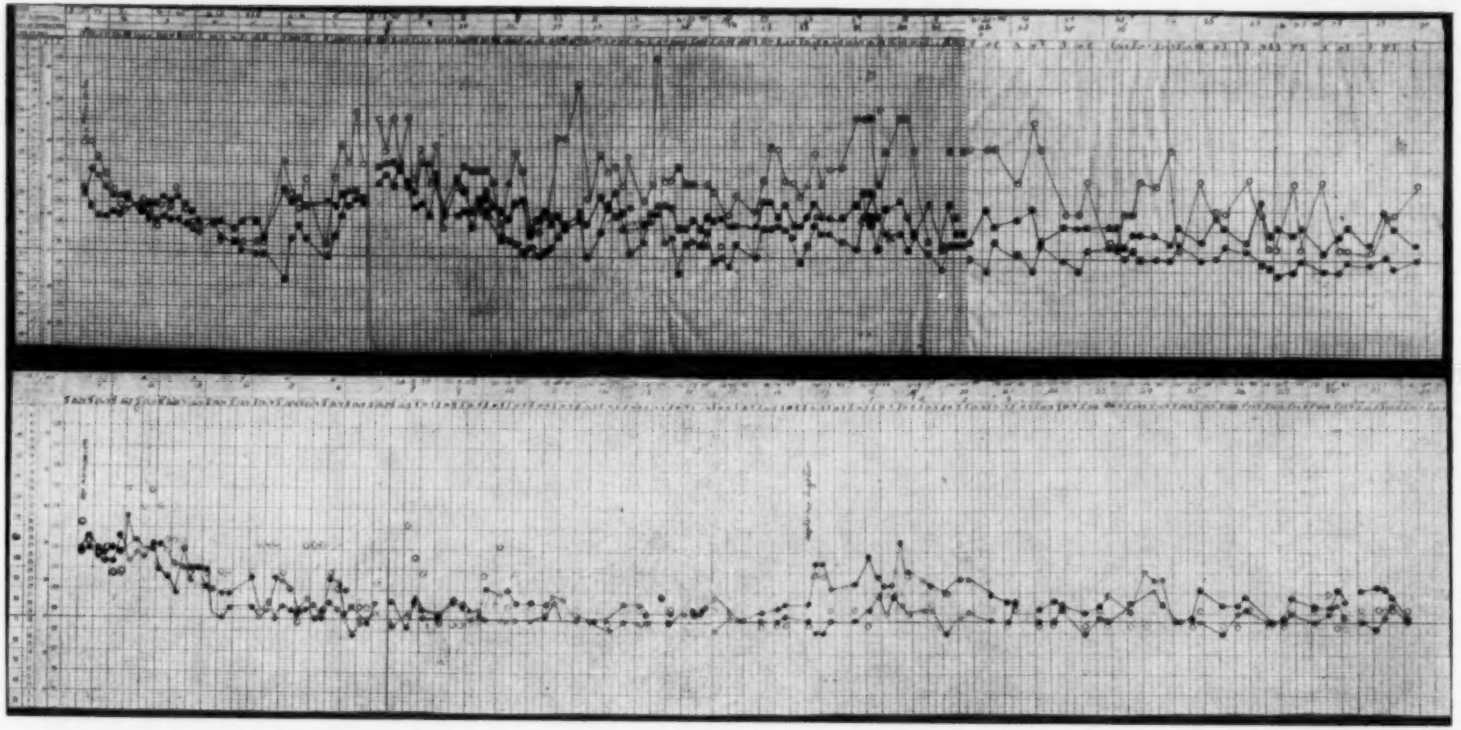

FIG. 3 (*above*). H. L. Clinical chart during first hospital admission, showing severe and prolonged clinical course of pulmonary disease.
FIG. 4 (*below*). H. L. Clinical chart during second hospital admission. Note normal temperature on December 11, 1945, the day on which femoral thrombosis was found.

piece it certainly was of a size sufficient to occlude the pulmonary artery and produce instant death.

When this patient was first admitted to the hospital, it was thought that he had some form of bronchopneumonia. It soon became apparent that the etiologic agent was not the pneumococcus. Repeated cultures of the sputum failed to reveal any specific organism, and specific therapy, first with sulfadiazine and later with penicillin, was conspicuously futile.

FIG. 5. Common femoral vein removed at operation on H. L. It is opened to demonstrate the extent of the thrombosis. The clear spaces represent areas where the thrombus fell out of the vein when it was opened.

In view of the roentgen finding of a fibrotic lesion in the extreme left apex of the lung and the repeated episodes of frank hemoptysis, the diagnosis of tuberculous bronchopneumonia was entertained, but reasonably excluded by the repeated failure to find tubercle bacilli in the sputum and by the subsequent course of events, characterized by recurring episodes of improvement and relapse. Primary atypical pneumonia was never considered to be a remote possibility, in view of the obvious severity of the infection, the persistent polymorphonuclear leukocytosis and the recurring hemoptysis. The diagnosis of chronic bronchiectasis was seriously entertained, because of the repeated episodes of pulmonary infection and hemoptysis, but there was nothing in the previous medical history, specifically no history of chronic cough or expectoration, to make such a diagnosis tenable.

There was nothing in this patient's previous history which offered an explanation for the femoral thrombosis which was discovered almost seven months after his first episode of pulmonary embolism, and which in retrospect must have been the source of pulmonary infarctions at intervals during all of this time. He had never had either typhoid fever or pneumonia. Either an attack of scarlet fever in childhood, or an insidiously developing thrombophlebitis secondary to a mild long-standing trichophytin infection of the feet, is more intriguing than probable from the standpoint of etiology. Had one been sufficiently alert to the possible presence of bland thrombosis at the time when this patient first complained of slight discomfort in the left calf on the seventeenth day of his first admission, the correct diagnosis might have been reached. Eventually, the demonstrable presence of palpable thrombosis of the left femoral vein led to the correct diagnosis and appropriate operative treatment.

A casual glance at the specimen removed at operation should convince even the most skeptical that its presence constituted an ever-present threat to life.

Summary and Conclusion

Emboli may reach the lungs either from thrombi formed in the right side of the heart, or from those having their origin in the systemic veins, particularly those of the lower extremities. Thrombosis of the leg veins may also result from thrombophlebitis complicating certain infections notably typhoid fever and pneumonia.

Thrombosis of the leg veins occurring postoperatively is a very frequent cause of pulmonary embolism. It is usually possible to prevent this potential catastrophe either by prophylactic bilateral femoral ligation in selected cases, or by prompt interruption of these veins at the first indication of bland thrombosis manifested either locally, or by sublethal episodes of pulmonary infarction and embolism.

The patient whose history is presented in this report had repeated attacks of pulmonary embolism during a consecutive period of almost seven months, and it was only in the last such episode that the correct diagnosis was reached, and then only because slight discomfort in the left thigh led to the discovery of palpable thrombosis in the left femoral vein. No cause for this thrombosis was apparent.

Operative removal of the common femoral vein and its contained thrombus resulted in prompt relief of symptoms. There have been no further episodes of pulmonary embolism since operation five months ago.

This case is reported in order to raise the level of clinical suspicion regarding the presence of bland thrombosis in all instances of atypical pulmonary disease exhibiting those symptoms and physical signs which suggest the possibility of pulmonary embolism.

Addendum

On June 28, 1946, this patient was readmitted to the University of Pennsylvania Hospital with acute thrombophlebitis of the left leg, which responded rapidly and favorably to anticoagulant therapy. On November 13, 1946, he developed cramp-like pain in the right leg, and on the following day he had pain in the chest, cough, fever, and chills. At this time he consulted Dr. Louis A. Soloff, who referred the patient to the Temple University Hospital. He presented signs of consolidation over the right lower lobe posteriorly, and tenderness to deep palpation over both upper legs anteriorly. The diagnosis of phlebothrombosis of the right leg, with pulmonary embolism, was made, and on November 20, 1946, under

spinal anesthesia, the right external and common iliac vessels were exposed by Dr. Burnett, and although no clot was found the common iliac vein was dissected and doubly ligated. The patient's convalescence was complicated by disruption of the wound on November 29, which required secondary suturing. He was discharged on December 12, 1946.

Dr. Freeman, the patient's family physician, reports that up to the present time (December, 1947) there have been no further episodes of phlebothrombosis or pulmonary embolism, and that the patient has remained in normal good health except for considerable edema of the right leg.

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PERIARTERITIS NODOSA WITH RECOVERY: REPORT OF AN UNUSUAL CASE APPARENTLY DUE TO SENSITIVITY TO SULFADIAZINE*

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PERIARTERITIS nodosa is a disease which is so uniformly fatal that instances of recovery merit special attention. The case herewith recorded is of particular interest because of its association with sensitivity to sulfadiazine, a drug which is now suspected of being antigenic and capable of producing widespread vascular lesions similar to those of periarteritis nodosa.[1, 2, 3] In addition, the extraordinary and rapid recovery of this patient following the administration of full doses of the offending drug makes the following details worthy of record.

CASE REPORT

J. S., a 17 year old white American student, was admitted to Multnomah Hospital on March 2, 1944 complaining of nose bleeds, sore throat, pains in the joints and back, and a skin rash. He had always enjoyed good health until two and a half months before his admission, at which time he developed a sore throat. He consulted a physician who prescribed sulfadiazine in doses of 15 grains (1.0 gm.) every four hours. The patient took this medication for approximately one week. The sore throat disappeared, and he returned to school feeling quite well. Approximately six weeks later, and one month before his admission to the hospital, he again developed a sore throat. He consulted the same physician who again placed him on sulfadiazine. He

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took the medication for about two days and then stopped it because it seemed to make him very ill. He promptly developed a skin rash and nose bleeds, became feverish, and felt tired and achy. The rash, at first erythematous, in a few days became purpuric. These symptoms, which began within 24 hours after he started the second course of the drug, persisted and increased progressively in severity until his admission to the hospital four weeks later.

On admission his oral temperature was 99.4°, pulse 100, respirations 30. He looked ill and was in considerable distress. He complained of severe pain in his shoulders, legs and back. A fading purpuric rash was noted over his lower extremities. There was no cyanosis or icterus. His optic fundi were normal. There was a large blood clot in the left nostril and remnants of dark blood were present in the posterior pharynx. His neck was not remarkable. There was no glandular enlargement. The lungs were clear, and the heart was normal in all respects, except for sinus tachycardia and a soft systolic murmur audible at the apex. Blood pressure was 156 mm. of Hg systolic and 92 diastolic. The abdomen was flat and soft. The lower pole of his right kidney was palpable and quite tender. There was marked tenderness in the right costovertebral region. The liver and spleen were not enlarged. Neurological examination revealed all findings within normal limits.

His urine on admission showed specific gravity 1.022, one plus albumin, no sugar, occasional pus cells and occasional red cells in the sediment. The throat culture showed no predominant organism and no hemolytic streptococci. The red cell count was 5,500,000 with 16 gm. of hemoglobin. The white cell count was 10,300 with 60 per cent neutrophiles, 3 per cent eosinophiles, 10 per cent small lymphocytes, 5 per cent monocytes and 4 per cent staff cells. The sedimentation rate was 3 in 15 minutes, 22 in 45 minutes (Westergren). The platelet count was 76,000; blood urea nitrogen was 14 mg. per cent.

He was given salicylates and codeine for pain and sodium pentobarbital for rest. Two days after his admission to the hospital his back pain became extremely severe. His blood pressure rose to 164/104. His pain was most intense in the neighborhood of the right costovertebral angle and seemed to radiate into the right flank. A large number of red cells appeared in his urine. Salicylates were stopped. The prothrombin time was 39 per cent of normal. He was placed on parenteral menadione, and two days later the prothrombin time had risen to 66 per cent of normal. Bleeding and coagulation times were within normal limits. Four days after admission he began to vomit, and for the next five weeks he retained very little food or fluid. His nutrition and his fluid and electrolyte balance were maintained largely by the intravenous route. He lost weight rapidly. His temperature ranged from 99.5° to 103° each day. His generalized muscle aches and pains became more intense.

On March 9, one week after admission to the hospital, he developed an acute epididymitis. He displayed migratory painful swelling of both shoulders and of his left elbow. His sore throat was very troublesome and interfered with his taking nourishment and fluids, and he vomited a great deal. On March 15, two weeks after admission, a biopsy of his left deltoid muscle was performed. The pathologic diagnosis was periarteritis nodosa (figure 1). The patient became very apprehensive and panicky, and his ever present fear of death complicated his nursing care. Red cells, albumin, and a few casts were present in the sediment of each of many urine specimens. He occasionally had gross hematuria. Hemoglobin ranged from 16.2 gm. to 14.4 gm., and red cells from 5.4 million to 4.0 million. The white cell count ranged from 10,300 to 19,900 and the polymorphonuclear neutrophile count ranged from 67 to 81 per cent. Three eosinophiles were recorded on one blood smear, and no eosinophiles on 17 other smears. The sedimentation rate remained quite rapid, and the platelet count varied from 76,000 to 147,000. Several electrocardiograms showed nothing but sinus tachycardia. One tracing showed depression of the ST segments in Leads I and II and

slurred QRS complexes. These findings were interpreted as evidence of an active myocardial process. The sternal marrow was aspirated on March 13 and showed an essentially normal cellular pattern, except for the myelocyte count which was at the upper limit of normal. Blood cultures, and serum agglutination tests for the typhoid-

FIG. 1. A small artery in the deltoid muscle showing inflammation and hyaline degenerative changes in the outer vessel wall. The outer coats and the perivascular area are infiltrated with round cells and polymorphonuclear leukocytes. The dark patch on the vessel is an artefact.

paratyphoid group and for *Brucella abortus,* were all negative. The Paul-Brunnell test was negative in a 1–4 dilution. A flat film of the abdomen taken on March 8 showed the right kidney shadow to be obscured. The left kidney appeared normal and no opaque calculi were seen.

On April 7, five weeks after his admission, his condition was desperate and it seemed as though he would soon die. On this date a house physician, apparently unfamiliar with the patient's history of sulfonamide sensitivity, resumed therapy with sulfadiazine! The patient was given one gram of the drug orally. Within 30 minutes he developed a generalized urticarial rash on his trunk and extremities, which responded to hypodermic epinephrine. The sulfadiazine was continued, one gram every four hours for five days. During this time, the patient had numerous urticarial eruptions which were controlled by repeated injections of epinephrine. On April 12, sulfadiazine was discontinued.

On April 14 he began to improve. He was able to retain all of his food. His temperature dropped appreciably to a daily peak of 99.5° and by April 16 it was normal and remained so. On April 19 he was able to sit in a wheel chair. He continued to show daily improvement and gained strength rapidly. The urine abnormalities cleared, and his pain subsided. He was discharged from the hospital on April 27. By June 15, 1944 he was able to enroll in summer school. He has been studied at frequent intervals since that time, and his examinations have all been completely negative. His blood pressure and urine have shown no abnormalities. In March, 1945, one year after the onset of his illness, he passed the Selective Service Examination. He was ultimately rejected by the Medical Board on the basis of his history. He was last thoroughly checked in August, 1946, 28 months after his recovery and was found to be in splendid health. He stated that he had not had a sick day since leaving the hospital.

On May 15, 1946, approximately two years after his recovery, an intradermal test for sulfonamide sensitivity was done, according to the technic described by Leftwich [4]: 0.1 c.c. of serum collected from an individual with a therapeutic blood sulfadiazine level, and 0.1 c.c. of control serum from the same individual without the drug were injected intradermally into the forearm of the patient. The sulfonamized serum produced a wheal of 13 mm. in 20 minutes; the control wheal was 12 mm. The test indicated no demonstrable sulfadiazine sensitivity. On August 6, 1946, .12 gm. (2 grains) of sulfadiazine was administered orally to the patient, and no reaction whatever was noted. A trial with full therapeutic doses of the drug was proposed, but the patient, recalling his previous experience, refused the test.

Since Kussmaul and Maier [5] first described periarteritis nodosa in 1866, reports of over 400 cases of the malady have appeared in the medical literature. The disease is usually first recognized at necropsy, but recently many cases have been confirmed antemortem by biopsy. An occasional case showing recovery or an unusually long remission has been recorded.[6]

Much attention has been directed in recent years to the striking similarity of the lesions and clinical features of periarteritis nodosa and those of anaphylactic reactions. The hypothesis of vascular allergy has been postulated by many observers [7] as the cause of the various phenomena present in this disease. Gruber [8] in 1923 suggested that periarteritis nodosa was a hypersensitization phenomenon involving the arterial walls and occurring during the course of the prolonged infection. Many other observers [9] have emphasized the frequency with which the disorder is associated with allergic phenomena, particularly asthma. Wilson and Alexander [10] checked the protocols of 300 consecutive cases of periarteritis nodosa reported in the literature and found bronchial asthma in 18 per

cent. These observers also emphasize that in many of the cases in which differential blood counts are recorded hypereosinophilia was present. Cohen, Kline, and Young [11] contend that periarteritis nodosa is a manifestation of clinical allergy of so severe a degree that irreversible destructive lesions occur in blood vessels. The milder vascular allergic reactions they feel, disappear without permanent tissue change; the more severe reactions are associated with tissue necrosis and are irreversible. Harkavy [12] presents a similar thesis and postulates that varying degrees of hyperergic vascular response determine the extent, and degree and reversibility of the lesions in the shock tissues affected.

In most instances bacterial allergies seem to be implicated, but Rich [1, 2, 3] has recently drawn attention to the possible rôle of other antigens which may produce such vascular lesions. He noted the widespread typical lesions of periarteritis nodosa in the viscera of necropsy cases in which there were definite histories of hypersensitivity to serum or to sulfonamides shortly before death. Furthermore, he was able to reproduce these lesions in rabbits following injections of large amounts of foreign serum. He was unable to sensitize his animals to sulfonamides because the drug apparently does not combine with plasma protein of rabbits to form a new molecule which is antigenic. However, Rich suggests that in humans sulfonamide drugs may be the inciting antigen and produce widespread vascular disease. He points out that there has been a marked increase in the number of cases of periarteritis nodosa coming to autopsy at the Johns Hopkins Hospital since the introduction of sulfonamides in 1936. He emphasizes the importance of a careful search for the inciting antigen in all cases of periarteritis nodosa that come under clinical observation. Labby and McDermott [13] have performed biopsies of muscles underlying the skin lesions produced by sulfonamide sensitivity and have found perivascular inflammatory lesions similar to the lesions of periarteritis nodosa.

In the case here reported, the relationship between the ingestion of the sulfonamide and the onset of the patient's illness seems more than coincidental. The initial dose of sulfadiazine was apparently the sensitizing dose. When the drug was again taken six weeks later the patient immediately became very ill and developed fever, a skin rash and other phenomena indicative of drug sensitivity. These symptoms did not subside but progressed rapidly to the fulminating illness described. A picture of widespread vascular injury was suggested by the nephropathy with hematuria and hypertension, the generalized muscle tenderness, the hemorrhagic phenomena involving the skin and mucous membranes, and the electrocardiographic evidence of myocardial damage. A diagnosis of periarteritis nodosa was established by biopsy. An extraordinary situation arose at the height of the patient's illness when he was given full doses of sulfadiazine and in spite of obvious sensitivity, the drug was continued for five days. Even more striking was the fact that the patient began to improve shortly after sulfadiazine was stopped. It is possible that coincidence alone explains the apparent striking therapeutic paradox of prompt recovery following the administration of an obviously noxious antigen. It is likewise possible that the sulfadiazine may have controlled an infectious agent to which the patient had become sensitive. Sulfonamides have had a fair and unsuccessful trial in the treatment of many cases of periarteritis nodosa and only one instance of apparent recovery after its use had been reported.[14] In the present case one might

speculate that the patient may have been desensitized by means of overloading with specific antigen. Urbach [15] quotes certain experiments of Besredka in which animals which had sustained macroshock type of anaphylactic reactions were reinjected after a short period of time with a multiple of the lethal dose of the antigen. The animals were found to be completely insensitive. Urbach [16] further states that "deallergization by means of antigen overloading" succeeds under certain circumstances when the reinjection dose brings on a severe anaphylactic shock that is not immediately fatal but is followed by death after one or two hours, or by ultimate survival of the animal after severe prolonged manifestations. He demonstrated by perfusion experiments that the organs of an animal thus exposed to long lasting shock may become deallergized for the duration of its life with the inhibition of the antigen-antibody reaction.

In the patient herein reported one might hypothesize on the basis of such experimental work that some type of satiation of antibodies occurred in the primary shock tissues. The result was clinical insensitiveness to the antigen which had been given in doses sufficient to produce a prolonged severe non-lethal anaphylactic vascular reaction.

Summary

1. A case of periarteritis nodosa with recovery is reported associated with and apparently caused by sensitization to sulfadiazine.

2. Prompt recovery seemed to follow a severe prolonged anaphylactic reaction produced by the unwitting administration of the drug at the height of the patient's illness.

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CHRONIC LEAD POISONING AND HYPERTENSION, WITH DEATH RESULTING FROM PERITONITIS; REPORT OF A CASE

By John Q. Griffith, Jr., M.D., F.A.C.P., and Ralph Jones, M.D.,
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Fouts and Page [1] were unable to produce arterial hypertension in two dogs poisoned with lead, and expressed doubt that lead was ever a cause of hypertension in man. Griffith and Lindauer,[2] however, were able to produce arterial hypertension in rats chronically poisoned with lead and this has been confirmed by Diaz-Rivera and Horn.[3] In the case here reported it is believed that chronic lead poisoning offers the best explanation for both the hypertension and the final fatal outcome.

Case Report

On February 16, 1943, a white girl, 20 years of age, was admitted to the medical ward of the Hospital of the University of Pennsylvania on the service of Dr. O. H. Perry Pepper. At that time her blood pressure was 240 mm. Hg systolic and 166 diastolic and she was blind. She had been previously admitted to two other hospitals.

Her history began at the age of 15 when, after participating in a game of basket-

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From the Robinette Foundation and the Medical Clinic of the Hospital of the University of Pennsylvania.

ball, she developed weakness and palpitation. This soon passed off but it was found at that time that her systolic blood pressure was 160. Six months later she was admitted to the first hospital, where it was found her blood pressure was 160/120, her heart was normal in size as shown by orthodiagram, electrocardiogram was normal, and ophthalmoscopic examination revealed only slight narrowing of the arteries. One year later she was readmitted to the first hospital. Blood pressure on admission was 170/130, but thereafter it varied from 150/110 to 200/156. Orthodiagram at that time revealed a heart larger than normal, but the electrocardiogram was still normal. Renal studies were again negative except for a few casts and white cells in the urine. Ophthalmoscopic examination this time showed narrow vessels and rather hazy disc margins. At that time therapy with potassium thiocyanate was begun, without improvement. It was being continued, however, when she was re-admitted one year later. This time systolic blood pressure ranged between 170 and 200 mm. of mercury, but diastolic pressure was fairly constant at about 150 mm. Ophthalmoscopic examination was reported as showing arteries definitely reduced in caliber, papilledema of 1 or 2 diopters, and a few fresh hemorrhages. Renal studies were still normal, and she was continued on thiocyanate. About that time (1940) she entered college, where she continued until 1942, with little complaint except occasional blurring of vision.

In September, 1942, she was admitted to the second hospital. Blood pressure was 220/175, her heart was enlarged. Ophthalmoscopic examination was said to show papilledema of 2 to 4 diopters, narrow arteries, and fresh hemorrhages and exudates. Renal studies were still satisfactory, the urea clearance showing 195 per cent of average normal function. A muscle biopsy from the gastrocnemius was reported to show arteriolar sclerosis. On October 13, 1942, bilateral lumbar sympathectomy and celiac ganglionectomy were performed. There was an immediate drop in blood pressure to 140/100, but within a few days it rose again to 220/160. On the fifth day postoperatively her vision began to fail, and within 48 hours she could distinguish only light and dark. Otherwise she felt reasonably well until three weeks prior to admission to the University Hospital, when she developed persistent diarrhea and loss of weight.

Upon admission, an unusual eye ground picture was described by Dr. Francis H. Adler, as follows: "The disc is definitely pale and the outlines are irregular and partly obscured by changes which probably represent coagulation necrosis and not simple edema. Throughout the whole posterior pole are hard white deposits. These are probably lipoid in nature. There are no cotton patches present and no hemorrhages. The arteries are very markedly reduced in size and many of the secondary branches have entirely disappeared. The whole picture is of endarteritis with occlusion of the central artery: it is not that of malignant hypertension. I doubt if this girl ever had a true papilledema. Diagnosis: The end stages of extreme endarteritis obliterans of the retinal arteries."

This report suggested to us the possibility of lead poisoning, and further studies were made along this line. Additional history revealed that the patient had spent all her life, except when away at school, living in a remodeled farmhouse with a water supply obtained directly from an adjacent well. The piping originally installed was entirely composed of lead, but one year before the patient's birth this was changed to iron piping, it was said, although it seemed fairly certain that the portion of pipe passing through the foundations and actually entering the house remained the original lead. The patient's grandmother had lived in this house and drunk this water for 50 years without harm, although some of this period undoubtedly predated the installation of the plumbing. However, her father had died before the age of 50 of "acute indigestion" and her mother had died before the age of 50 with Bright's disease and hypertension. She had two brothers, aged 18 and 19 years, who were known to have blood pressures, respectively, as high as 180 and 150 systolic. Examination of the patient's

blood showed basophilic stippling, to the extent of 2 per cent, and the blood of one brother, the only one who could be reached, also showed basophilic stippling. Examination of the patient's blood for lead showed 0.070 mg. of lead per 100 gm. of blood in sample A, and 0.070 mg. in sample B. By the method used [4] the average normal figure (i.e. for subjects not poisoned by lead nor exposed beyond casual daily contacts) is 0.030 mg. of lead per 100 gm. of blood, and only one of a series of 73 normal subjects exceeded 0.050 mg. Roentgen-ray of bones did not show any changes attributable to lead.

Other studies included a blood urea nitrogen of 17 mg. per cent and a urea clearance of 50 per cent average normal function. Urinalysis showed abundant albumin, hyaline casts and white cells. Gastric acidity was normal. Gastrointestinal series showed abnormal motility with an increased rate of emptying of the lower ileum, and granular thickening of the walls of the cecum and ascending colon. Stool examination showed no parasites.

Her course was progressively downward. One month after admission fluid was found in the left chest and removed by thoracentesis. Vomiting and diarrhea became intractable and were the eventual cause of death which occurred on May 5, 1943.

Necropsy was performed 12 hours after death. Multiple ulcerations were found in the ileum, one of which had ruptured with resulting peritonitis, and this was thought to be the immediate cause of death. The lungs showed passive congestion and edema. The kidneys were grossly normal, but microscopically they showed changes indicative of nephrosclerosis.

Comment

Unusual features include: (1) The height of the blood pressure as compared with the relatively few symptoms attributable to it. (2) Blindness occurring following sympathectomy, and the unusual eye grounds. (3) The terminal picture with enteritis and peritonitis. (4) The elevated level of blood lead, the basophilic stippling, the history of possible source of lead poisoning and the family history.

It seems to us that lead poisoning is a possible explanation for the entire picture, and the only single explanation that can be offered. Fishberg [5] describes cases where blindness has occurred in acute lead poisoning, where the blindness is thought to be due to spasm of the retinal arteries with occlusion. While our patient was certainly not an example of acute lead poisoning, the increased blood lead concentration definitely establishes exposure to lead considerably in excess of that usually found. This exposure, extending from the pre-natal period through childhood, may well have left the patient vulnerable to crises such as that resulting from the sympathectomy, accompanied by acidosis or other profound metabolic disturbance. Sudden mobilization of lead is known to result from acidosis and other disturbances of homeostasis. Sympathectomy has been shown by McGrath [6] and later by Griffith, Comroe and Zinn [7] to increase greatly the susceptibility of blood vessels in animals poisoned with ergotamine tartrate, a poison also capable of producing endarteritis obliterans. It is possible that a sympathectomized area may also be more vulnerable to lead, and that this may account for the unusual severity of the enteritis, presumably due to lead, following the sympathectomy.

Acknowledgment: Lead determinations were done by T. V. Letonoff, M.S., of the Biochemical Laboratory, Philadelphia General Hospital. We acknowledge with thanks the cooperation of Dr. John G. Reinhold.

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EDITORIAL

A NEW RICKETTSIAL DISEASE

DURING the year 1946 many cases of an acute febrile infection of unusual character were observed in New York City.[1, 2] Most of these cases occurred in a group of apartment houses in a small area in Regency Park (Borough of Queens) housing 543 families, although similar cases were subsequently reported from three other boroughs. The clinical picture was so characteristic and the etiological features so interesting that the disease merits some attention.

The onset in most cases was abrupt with malaise, fever, usually chills and sweats, headache, pain in the orbits, and severe aching in the back and muscles which are reminiscent of a severe influenzal infection.

In about two-thirds of the cases the patients had noticed a localized cutaneous lesion several days before the onset of the fever. This was described as a pimple, boil or insect bite, although none had observed the biting. The lesion started as a small firm papule which gradually enlarged (0.5 to 1.5 cm. or more in diameter) and became vesicular; later there was central necrosis with the formation of a blackish eschar, but there was virtually no local pain or tenderness. Some erythema appeared in the skin about the lesion, and as a rule there was some enlargement of the regional lymph nodes but no obvious lymphangitis. This lesion healed in the course of about three weeks. It might be found on almost any part of the body but was usually on a covered portion. This premonitory initial lesion appears to be a virtually constant feature since it was found when searched for in nearly every patient who was observed during the active stage of the infection.

Either coincident with the onset of the fever or usually within 48 hours after this, a rash appeared. This consisted of a limited number (five to 100 or more, usually 20 to 40) of small, discrete, firm, erythematous papules somewhat resembling the initial lesion but with a diameter only one-half to one-third as great. Within a day or two in most cases a small firm vesicle appeared in the apex of the papule. Later this dried, often a small eschar formed, and after about four to seven days it healed without scarring. There was no itching or discomfort. The rash had no characteristic distribution except that it did not appear on the palms and soles and rarely on the mucous membranes.

The fever was typically remittent, the temperature often reaching 103° to 104° F., and it was accompanied by marked lassitude or prostration. It fell by lysis after an average duration of about one week, and all patients recovered without complications or sequelae. Except for occasional anor-

[1] SUSSMAN, L. N.: Kew Gardens' spotted fever, New York Med., 1946, ii, 27–28 (August 5).

[2] SHANKMAN, B.: Report on an outbreak of endemic febrile illness, not yet identified, occurring in New York City, New York State Jr. Med., 1946, xvi, 2156–2159.

exia or nausea, gastrointestinal disturbances were rare, and no patient showed any significant respiratory symptoms.

There was generally a moderate granulocytopenia, but otherwise the usual laboratory examinations showed nothing significant. In particular there was no agglutination of Proteus OX19, OX2 or OXK (except feeble reactions in a few cases).

Because of a slight resemblance to chickenpox, for which some of the cases had been mistaken, the name "rickettsialpox" was proposed by Greenberg et al.,[3] who have published an excellent description of the disease. Although the character of the eruption justifies the use of the term, pox, the resemblance to chickenpox is really superficial, and a clinical differentiation should usually be simple.

Studies carried out at the National Institute of Health in coöperation with the New York City Department of Health have revealed the agent causing the infection and important evidence regarding its transmission. By intraperitoneal inoculation of mice with blood obtained in the acute stage of the disease, Huebner et al.[4] isolated from each of two patients an organism which proved to be a rickettsia. This was maintained by serial passages in mice and guinea pigs, and in the latter species it excited an inflammatory reaction of the scrotum somewhat resembling that caused by the rickettsia of endemic typhus. It also grew luxuriantly in the yolk sac of fertile eggs, causing death of the embryos, but it could not be cultivated in any ordinary (lifeless) culture media.

These investigators prepared an antigen from the yolk sac cultures by the method of Topping and Shepard and utilized this for complement fixation tests by the Bengtson method with the serum of convalescent patients and of guinea pigs which survived infection. In all the cases reported a positive reaction was obtained, and in the four cases in which a comparison was possible, the serum during convalescence showed a much higher titer than that obtained during the early stage of the disease.

By making "cross tests" with immune serum and antigens similarly prepared from other species of rickettsia, they showed that this strain was antigenically distinct from the agents causing endemic typhus fever, tsutsugamushi (scrub typhus) and Q fever. There was, however, a rather marked cross reaction with the antigen of Rocky Mountain spotted fever. They regard the organism as a distinct species and proposed for it the name *Rickettsia akari*.

Investigation of the premises in which some of these cases occurred showed that mice were numerous and that the basements were heavily infested with the rodent mite *Allodermanyssus sanguineus*. This observation and the fact that no other vermin was found suggested that the urine and the

[3] Greenberg, M., Pelliteri, O., Klein, I. F., and Huebner, R. J.: Rickettsialpox, Jr. Am. Med. Assoc., 1947, cxxxiii, 901–906.

[4] Huebner, R. J., Stamps, P., and Armstrong, C.: Rickettsialpox—a newly recognized rickettsial disease. I. Isolation of the etiological agent, Pub. Health Rep., 1946, lxi, 1605–1614.

mites might constitute respectively the reservoir and the vector of the infection. Huebner et al.[5] succeeded in isolating from these mites two strains of rickettsiae which were identical in morphology, pathogenicity and antigenic properties with the human strains. One was obtained from a guinea pig which had received an intraperitoneal injection of ground-up mites and the other from a young mouse on which mites had been allowed to engorge. Huebner et al.[6] also isolated a similar strain from a mouse which was trapped on the premises. One of the investigators who had collected and processed the mites developed a typical attack of the disease three weeks later. The evidence is, therefore, strong that the infection was native in the mice and that it was conveyed from mouse to mouse and from mouse to man by these mites.

Further observation will be required to determine the practical importance of the infection and its precise relation to other rickettsial diseases. Nothing is known as to the distribution of the infection among mice. It appears to have been prevalent among mice at the location of the epidemic, since mice trapped there were mostly refractory to inoculation, and four of seven mice tested gave positive complement fixation reactions. Laboratory white mice and house mice trapped in Virginia, on the other hand, were usually susceptible to inoculation and gave negative serum reactions.

Little is known as to the distribution of the vector. Muesebeck is quoted [5] as stating that specimens of this mite have been collected from Tucson, Ariz., Indianapolis, District of Columbia, New York City, Philadelphia and Boston. It seems likely, therefore, that it may be found widely distributed if a systematic search is made.

The disease resembles tsutsugamushi in having a mite as a vector and in showing an eschar at the site of the bite. The latter infection, however, is a severe one with a high mortality, and the agents are antigenically distinct. The rash of rickettsialpox is also radically different, as it is, indeed, from that of all other known rickettsial infections. *Rickettsia akari* seems to be closely related antigenically to *R. rickettsiae* of Rocky Mountain spotted fever. The latter, however, is a severe infection with a high mortality, there is no local eschar, and the rash is quite different.

This infection seems to resemble most closely the fièvre boutonneuse of the Mediterranean region, the agent of which is named *R. conori*. This is likewise a mild infection, and there is usually a local eschar, although the vector is reported to be a tick and the reservoir of infection the dog. No direct comparison of these organisms as to their antigenic relationships has been published, but as *R. conori* has been reported [7] to show complete cross

[5] HUEBNER, R. J., JELLISON, W. L., and POMERANTZ, C.: Rickettsialpox—a newly recognized rickettsial disease. IV. Isolation of a rickettsia apparently identical with the causative agent of rickettsialpox from *Allodermanyssus sanguineus*, a rodent mite, Pub. Health Rep., 1946, lxi, 1677–1682.

[6] HUEBNER, R. J., JELLISON, W. L., and ARMSTRONG, C.: Rickettsialpox—a newly discovered rickettsial disease. V. Recovery of *Rickettsia akari* from a house mouse (*Mus musculus*), Pub. Health Rep., 1947, lxii, 777–780.

[7] BADGER, L. F.: Rocky Mountain spotted fever and boutonneuse fever, a study of their immunological relationships, Pub. Health Rep., 1933, xlviii, 507–511.

immunity with *R. rickettsiae,* it seems probable that it is also related to *R. akari.* Such relationships suggest that these three species may be relatively recent variants of a common ancestor. Caminopetros (1932) has described scrotal reactions in guinea pigs infected with *R. conori* which seem to resemble those caused by *R. akari.* There appear, however, to be differences in the pathogenicity of the two rickettsiae for other animals; the cutaneous eruptions they produce in man are different; and *R. conori* excites the production of agglutinins for strains of Proteus X,[8] whereas *R. akari* does not. The investigators, therefore, seem justified in regarding *R. akari* as a distinct species.

If this epidemic proves to be merely an unusual and fortuitous transfer of a rodent infection to man, it is, perhaps, primarily a matter of scientific interest. If, however, it proves to be widely distributed, even though mild and sporadic in occurrence, like endemic typhus, it becomes a problem of immediate practical importance. This point might be settled simply, by a search for cases of the disease. The clinical manifestations are so distinctive that it should be recognized easily if the observer is familiar with it. One not familiar might well ignore sporadic cases of so mild an infection, dismissing them as "atypical chickenpox" or as a "skin rash" of minor importance. It is stated [5] that some of the mites of this species, collected in other localities, had been taken on man, and were noted as "causing rash." It is, indeed, probable that the nature of the disease in New York City would not have been discovered if it had not occurred in epidemic form.

P. W. C.

[8] DURAND, P.: La reaction de Weil-Félix dans le fièvre boutonneuse, Arch. Inst. Pasteur de Tunis, 1932, xx, 395–421.

REVIEWS

Rh: Its Relation to Congenital Hemolytic Disease and to Intragroup Transfusion Reactions. By EDITH L. POTTER, M.D., Ph.D., Asst. Prof. of Pathology, Department of Obstetrics and Gynecology, The University of Chicago and The Chicago Lying-In Hospital. 344 pages; 14.5 × 21 cm. The Year Book Publishers, Inc., Chicago, Illinois. 1947. Price, $5.50.

Dr. Potter has performed a great service for the medical profession in preparing this monograph on the Rh factor. In the seven years since its discovery by Landsteiner and Weiner, a tremendous literature has developed as evidenced by the bibliography of over 700 references cited by the author. The material presented is discussed with authority based upon the author's personal experiences as well as upon careful analysis of the literature. In spite of the fact that many aspects of the subject are still in a state of flux, as the author points out, a sufficient bedrock of permanent data has now been established which is of importance to anyone concerned with blood transfusion therapy, or the care of the pregnant woman and her infant in the neo-natal period. Historical and technical material is exhaustively covered and there is an admirable consideration of the pathology of congenital hemolytic disease. The reviewer, incidentally, is entirely in sympathy with the use of the term congenital hemolytic disease as opposed to the less descriptive and often misused term, erythroblastosis fetalis. The publishers have provided a pleasing format. The book is highly recommended to those seeking a general acquaintance with the subject, as well as to those more specifically interested in the field.

M. S. S.

If You Ask My Advice: Frank Discussions of Family Problems. By HENRY PLEASANTS, JR., M.D. 110 pages; 21 × 14 cm. 1946. Bruce Humphries, Inc., Boston. 1946. Price, $2.00.

This book is a short one designed to give advice to lay people on a number of topics related to psychiatry, with chapter headings such as: Insanity in the Family, The Problem Child, Child Discipline, The Alcoholic, The Drug Addict. As is usual when books are written on specialized scientific topics by persons with little or no knowledge of the topic, there is a generous sprinkling of misinformation. This book is no exception. This reviewer could not recommend this book to anyone either lay or professional.

H. W. N.

Developmental Diagnosis: Normal and Abnormal Child Development—Clinical Methods and Pediatric Applications. (2nd Edition, Revised and Enlarged.) By ARNOLD GESELL, M.D., and CATHERINE S. AMATRUDA, M.D. 496 pages; 24 × 16 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1947. Price, $7.50.

In this effective revision of the first edition, the authors have enlarged both the extent and depth of the material contents. Case examples, drawn from the Yale Clinic of Child Development, are provided illustrative of the many diagnostic problems discussed. The first part of the volume deals with basic principles of child development, behavior characteristics and their growth patterns from four weeks to three years. Norms of development, photo tracings along with developmental tests are provided to strengthen the practical value of the volume. The second section of the volume deals with deviates from the authors' norms of normal development. The

problem of amentia is discussed at great lengths, both etiologically and symptomatologically, followed by the possible effects of these defects on performance, total development and overall personality pattern. Included are two chapters concerning the neurological aspects of infant development along with effects of cerebral injuries. The third section of the volume discusses the rôle of private medical and public health in guarding the growth of the early child. The volume is completed with six appendices summarizing the examination technic, charts of growth trends, equipment lists, use of cinema equipment, and suggested readings. The volume will be of interest to those in close contact with the young child, both as a textbook and handy reference.

H. W. N.

The Clinical Examination of the Nervous System. 8th Ed. By G. H. MONRAD-KROHN, M.D., F.R.C.P., Professor of Medicine in the Royal Frederick University, Oslo, etc. 380 pages; 13 × 19 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper and Brothers. 1947. Price, $4.50.

This eighth edition has been revised and improved. It is written for medical students so that they may learn to perform an orderly and comprehensive neurological examination. It covers the nervous system in a brief but adequate manner. The photographs are well done to illustrate various lesions and the diagrams are well placed. The roentgenograms and arteriograms are exceptionally well reproduced.

No attempt is made to correlate and interpret the neurological findings. Neurological diseases are not discussed. The student will find this book a very valuable adjunct to his library. It is a ready reference book.

W. L. F.

BOOKS RECEIVED

Books received during November are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Blood Derivatives and Substitutes: Preparation, Storage, Administration and Clinical Results Including a Discussion of Shock: Etiology, Physiology, Pathology and Management. By CHARLES STANLEY WHITE, M.D., ScD., Former Professor of Surgery, George Washington University School of Medicine, etc., and JACOB JOSEPH WEINSTEIN, B.S., M.D., Associate in Surgery, School of Medicine, George Washington University. 484 pages; 23.5 × 16.5 cm. The Williams & Wilkins Company, Baltimore. 1947. Price, $7.50.

Conference on Metabolic Aspects of Convalescence: Transactions of the Thirteenth Meeting. Edited by EDWARD C. REIFENSTEIN, JR., M.D., Massachusetts General Hospital, Boston. 232 pages; 23 × 15 cm. (paper-bound). Conference sponsored by Josiah Macy, Jr., Foundation, New York. 1946. Price, $2.00.

Conference on Metabolic Aspects of Convalescence: Transactions of the Fourteenth Meeting. Edited by EDWARD C. REIFENSTEIN, JR., M.D., Sloan-Kettering Institute, New York. 190 pages; 23 × 15 cm. (paper-bound). Conference sponsored by Josiah Macy, Jr., Foundation, New York. 1946. Price, $2.25.

Differentialdiagnose der Lungenrontgenbilder: Besondere Berucksichtigung derjenigen Erkrankungen die mit der Lungentuberkulose verwechselt werden konnen. By DR. MED. RUDOLPH ZEERLEDER. 296 pages; 24 × 16 cm. Medizinischer Verlag Häns Huber, Bern. 1947. Price, fr. 28.

Diseases of the Nervous System. 3rd Ed. By W. RUSSELL BRAIN, D.M. (Oxon.), F.R.C.P. (London), Physician to the London Hospital, etc. 987 pages; 22 × 14.5 cm. Oxford University Press, New York. 1947. Price, $10.75.

Diseases of the Nose, Throat and Ear. 9th Ed., Revised. By WILLIAM LINCOLN BALLENGER, M.D., F.A.C.S., Late Professor, School of Medicine, University of Illinois; and HOWARD CHARLES BALLENGER, M.D., F.A.C.S., Associate Professor and Acting Chairman of the Department of Otolaryngology, Northwestern University School of Medicine, Chicago, etc.; assisted by JOHN JACOB BALLENGER, B.S., M.D., Research Fellow in Otolaryngology, Northwestern University School of Medicine, Chicago. 993 pages; 24 × 16 cm. Lea & Febiger, Philadelphia. 1947. Price, $12.50.

The Foot and Ankle: Their Injuries, Diseases, Deformities and Disabilities. 3rd Ed., Revised. By PHILIP LEWIN, M.D., F.A.C.S., Associate Professor of Bone and Joint Surgery, and Acting Head of Department, Northwestern University Medical School, etc. 847 pages; 24 × 16 cm. Lea & Febiger, Philadelphia. 1947. Price, $11.00.

History of Medicine: A Correlative Text, Arranged According to Subjects. By CECILIA C. METTLER, A.B., Ed.B., A.M., Ph.D., Late Assistant Professor of Medical History, Univ. of Georgia, School of Medicine, etc.; edited by FRED A. METTLER, A.M., M.D., Ph.D., Associate Professor of Anatomy, College of Physicians and Surgeons, Columbia University. 1215 pages; 24 × 16 cm. The Blakiston Company, Philadelphia. 1947. Price, $8.50.

Jaundice: Its Pathogenesis and Differential Diagnosis. By ELI RODIN MOVITT, M.D., Acting Chief of Medicine, Veterans Administration Hospital, Oakland, California, etc. 261 pages; 24 × 16 cm. Oxford University Press, New York. 1947. Price, $6.50.

Neutron Effects on Animals. By THE STAFF OF THE BIOCHEMICAL RESEARCH FOUNDATION, DR. ELLICE MCDONALD, Director, Newark, Delaware. 198 pages; 23.5 × 16 cm. The Williams & Wilkins Company, Baltimore. 1947. Price, $3.00.

A Primer of Cardiology. By GEORGE E. BURCH, M.D., F.A.C.P., Associate Professor of Medicine, Tulane University School of Medicine, etc., and PAUL REASER, M.D., Instructor in Medicine, Tulane University School of Medicine, etc. 272 pages; 24 × 15.5 cm. Lea & Febiger, Philadelphia. 1947. Price, $4.50.

Procedure in Examination of the Lungs, with Especial Reference to the Diagnosis of Tuberculosis. 3rd Ed. By ARTHUR F. KRAETZER, M.D., Associate Attending Physician, Lenox Hill Hospital, etc. Revised and with a Preface by JACOB SEGAL, M.D., F.A.C.P., F.C.C.P., Medical Director, Los Angeles Sanatorium, etc. 150 pages; 21 × 14 cm. The Oxford University Press, New York. Price, $3.50.

Recent Advances in Medicine: Clinical; Laboratory; Therapeutic. 12th Ed. By G. E. BEAUMONT, M.A., D.M. (Oxon.), F.R.C.P., D.P.H. (Lond.), Physician to the Middlesex Hospital, etc., and E. D. DODDS, M.V.O., D.Sc., Ph.D., M.D., F.R.C.P., F.R.I.C., F.R.S. (Edin.), Courtauld Professor of Biochemistry in the University of London, etc. 422 pages; 21 × 13.5 cm. The Blakiston Company, Philadelphia. 1947. Price, $6.00.

Surgical Disorders of the Chest: Diagnosis and Treatment. 2nd Ed. By J. K. DONALDSON, B.S., M.D., F.A.C.S. (Lt. Col., A.U.S.), Diplomate American Board of Surgery; etc. 485 pages; 24 × 16 cm. Lea & Febiger, Philadelphia. 1947. Price, $8.50.

Ulcer: The Primary Cause of Gastric and Duodenal Ulcer—Diagnosis, Medical and Surgical Treatment, Prevention. By DONALD COOK, B.A., M.D., Chicago. 187 pages; 22.5 × 14 cm. Medical Center Foundation and Fund, Chicago. 1946. Price, $5.00.

Unipolar Lead Electrocardiography: Including Standard Leads, Unipolar Extremity Leads and Multiple Unipolar Precordial Leads. By EMANUEL GOLDBERGER, B.S., M.D., Adjunct Physician, Montefiore Hospital, New York, etc. 182 pages; 24.5 × 16 cm. Lea & Febiger, Philadelphia. 1947. Price, $4.00.

COLLEGE NEWS NOTES

A.C.P. Postgraduate Courses

During 1947 more than 1,000 physicians, the great majority of them Fellows and Associates of the College, were registered in one or more courses.

The quality of the College courses has been constantly improved through continued experience. A great host of the registrants feel that the conduct of these courses constitutes the most important activity of the College and it is almost the universal opinion, expressed by the registrants, that these courses are the finest available in America. The Dean of a prominent medical school recently said that the College postgraduate program would be one that any medical school would be very proud to foster.

The registration in the Autumn, 1947, was as follows:

No.	Title	Institution	Director	Registration
1	Internal Medicine	University of Pittsburgh School of Medicine	R. R. Snowden	20
3	Mechanics of Disease	Peter Bent Brigham Hospital, Boston	George W. Thorn	26
4	Hematology—Blood Disorders	Boston Institutions	William B. Castle	48
5	Physiological Basis for Internal Medicine	University of Pennsylvania Graduate School of Medicine, Philadelphia	Julius H. Comroe, Jr.	189
6	Advanced Cardiology	Southwestern Medical College, Dallas	Tinsley R. Harrison	38
8	Internal Medicine	University of Wisconsin Medical School, Madison	William S. Middleton	27
9	Recent Advances in the Diagnosis and Treatment of Cardiovascular Disease	Massachusetts General Hospital, Boston	Paul D. White	89
10	Gastro-enterology	Graduate Hospital of the University of Pennsylvania, Philadelphia	Henry L. Bockus	41
11	Cardiovascular Disease	Yale University School of Medicine, New Haven	H. M. Marvin	28

Courses No. 2, Psychosomatic Medicine, at the University of Colorado School of Medicine, Denver; No. 7, Chemotherapy—New Drugs, at Boston University School of Medicine; and No. 12, General Medicine, at the University of Texas School of Medicine, Galveston, were cancelled.

Spring, 1948 Schedule of Courses

No. 1, Medical Aspects of Radioactive Substances—Naval Medical Center, Bethesda, Md.; February 17–27. (First week devoted to nuclear physics, and optional; physicians may register only for second week, February 23–27, if desired.)

No. 2, PHYSICAL MEDICINE—Mayo Clinic, Rochester, Minn.; Director, Frank H. Krusen, M.D., F.A.C.P.; March 22–27.

No. 3, CARDIOLOGY—University of Southern California School of Medicine, Los Angeles; Director, George C. Griffith, M.D., F.A.C.P.; April 12–17.

No. 4, ELECTROCARDIOGRAPHY: BASIC PRINCIPLES AND INTERPRETATION—Massachusetts General Hospital, Boston; Director, Conger Williams, M.D.; May 10–15.

No. 5, INTERNAL MEDICINE—Gallinger Municipal Hospital, Washington, D. C.; Director, Wallace M. Yater, M.D., F.A.C.P.; May 17–22.

No. 6, CLINICAL ALLERGY—Roosevelt Hospital, New York City; Director, Robert A. Cooke, M.D., F.A.C.P.; May 17–29.

No. 7, CLINICAL NEUROLOGY—Jefferson Medical College, Philadelphia; Director, Bernard J. Alpers, M.D., F.A.C.P.; May 24–29.

No. 8, PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE—University of Illinois Medical School, Chicago; Director, A. C. Ivy, M.D., F.A.C.P.; May 31–June 5.

No. 9, DIABETES AND METABOLIC DISEASES—New England Deaconess Hospital, Boston; Director, Elliott P. Joslin, M.D., F.A.C.P.; July 12–16.

Fees for all courses, with the exception of No. 6, will be $30.00 per week to A.C.P. members, and $60.00 to non-members. No fee will be charged to medical officers in the Army or Navy in the case of Course No. 1. The fee for Course No. 6, which is purely a clinical course limited to eight physicians, will be $60.00 per week to A.C.P. members, and $120.00 to non-members.

Course No. 3 is specifically organized as a pre-Convention course at Los Angeles during the week just preceding the 29th Annual Session of the College at San Francisco, April 19–23, and will afford an opportunity to members to take this course on the West Coast just before attending the Annual Meeting of the College.

Detailed Bulletins of each course will be published in early January and distributed to all members of the College and to non-members requesting copies. Inquiries should be addressed to the Executive Secretary, The American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

AMERICAN COLLEGE OF PHYSICIANS RESEARCH FELLOWSHIPS IN MEDICINE
1948 AWARDS

The Board of Regents of the College, on nomination of the Committee on Fellowships and Awards, awarded six Research Fellowships in Medicine for the year beginning July, 1948, at their meetings in Philadelphia on November 22 and 23, 1947. The awards were made to the following physicians.

CHARLES GORDON CAMPBELL, M.D., C.M., Vancouver, B. C., Can. Dr. Campbell attended the University of British Columbia and is a graduate of the McGill University Faculty of Medicine, 1945. He interned in the Royal Victoria Hospital, Montreal, 1945–46, and has held appointments in the Vancouver General Hospital as Assistant Resident in Medicine, 1946–47, and as Fellow in Cardiology, 1947–48. Dr. Campbell will undertake studies of the basic physiology of certain cardiovascular problems in the Department of Physiology of McGill University, under the supervision of Professor Hebbel E. Hoff.

FRANK HERBERT GARDNER, M.D., San Bernardino, Calif. Dr. Gardner attended Northwestern University (B.S., 1941; M.D., 1944). He served as intern and Assistant Resident in the San Francisco Hospital, 1944–46, and as Senior Assistant Resident in the University of California Hospital, 1946–47. Presently Fellow in Medicine in the Boston City Hospital, Dr. Gardner will conduct studies in the Thorndike Memorial Laboratory under the direction of William B. Castle, M.D., F.A.C.P., and Thomas H. Ham, M.D., F.A.C.P., of the mechanism and clinical application of the osmotic fragility test.

SAMUEL P. MARTIN, M.D., Durham, N. C. Dr. Martin's premedical and medical courses were taken at Washington University, St. Louis, where he received the M.D. degree in 1941. He interned in the Barnes Hospital, St. Louis, 1942–43, and served there also as Assistant Resident in Medicine, 1943–44. Dr. Martin served in the Army from 1944 until 1947. He is presently Resident in Medicine in the Duke University Hospital. With the aid of the Fellowship, Dr. Martin will undertake studies of bacterial metabolism in the Rockefeller Institute for Medical Research, New York, N. Y., under the direction of Dr. René J. Dubos.

PERITZ SCHEINBERG, M.D., Miami, Fla. Now Assistant Resident in Medicine in the Duke University Hospital, Dr. Scheinberg attended Emory University, where he received the A.B. degree in 1941, and the M.D. degree in 1944. He subsequently served as intern and Assistant Resident in Medicine in the Grady Memorial Hospital, Atlanta, Ga. Dr. Scheinberg served in the U. S. Naval Reserve, 1945–46. He will conduct an investigation of cerebral circulation and peripheral vascular flow in normal and hypertensive persons in the Duke University Hospital under the direction of Eugene A. Stead, Jr., M.D., F.A.C.P.

LUTFU LAHUT UZMAN, M.D., Istanbul, Turkey. Dr. Uzman will conduct studies, now under way, with Dr. J. Folch-Pi, in the Department of Scientific Research of the McLean Hospital, Waverley, Mass., on the isolation and characterization of brain proteins and their rôle in health, disease and senescence. Dr. Uzman received the B.S. degree from the University of Istanbul Faculty of Science in 1940. Following several years of study in the Medical School of that institution, he transferred to the Harvard Medical School and completed his work for the M.D. degree there in 1946. He interned in the Boston City Hospital, Neurology Service, 1946–47, and has since held appointment as Assistant in the McLean Hospital.

JOHN MARTIN WELLER, M.D., Ann Arbor, Mich. Dr. Weller completed his undergraduate studies at the University of Michigan in 1940 and received the M.D. degree from Harvard Medical School in 1943. He served as Medical House Officer, Peter Bent Brigham Hospital, Boston, from January to October, 1944; as Assistant Resident in Medicine in the Vanderbilt University Hospital, Nashville, Tenn., from October, 1944, to July, 1945. Since January of 1946, Dr. Weller has been Medical Resident in the Veterans Administration Hospital, Hines, Ill. Dr. Weller's appointment to the first Alfred Stengel Research Fellowship of the American College of Physicians will enable him to undertake, with Professor A. Baird Hastings in the Department of Biologic Chemistry of Harvard Medical School, studies concerning the ionic patterns of the intracellular fluids and their influence on enzymatic reactions; of acid-base balance in tissues other than skeletal muscle tissue.

The American College of Physicians takes pleasure in announcing that on December 3, 1947, Frank McLeod Wiseley, M.D., F.A.C.P., Findlay, Ohio, became a Life Member.

The Fourth Annual Clinical Conference of the Chicago Medical Society will be held at the Palmer House, Chicago, March 2–5, 1948. The Conference will consist of lectures, panel and round-table discussions, and clinico-pathologic seminars. Scientific and technical exhibits will be a feature of the meeting. Physicians, whether general practitioners or specialists, are invited to attend the Conference. Hotel reservations may be made directly with the Palmer House.

SPECIALTY BOARD EXAMINATIONS

American Board of Dermatology and Syphilology, Inc., 66 E. 66th St., New York 21, N. Y.; George M. Lewis, M.D., Secretary-Treasurer. Oral examinations

for Group A and B candidates will be held in Philadelphia, April 2–4, 1948. Written examinations for Group B will be given on February 16, 1948, in various cities in the United States.

At the meeting of the Board in Chicago, October 24–26, 1947, there were 81 candidates, of whom 55 were successful. There are now 924 certified diplomates on the roster of the American Board of Dermatology and Syphilology, Inc.

American Board of Internal medicine, 1 W. Main St., Madison 3, Wis.; William A. Werrell, M.D., Assistant Secretary-Treasurer. Oral examinations will be conducted at San Francisco in April, 1948, and in Chicago in June, 1948, both periods immediately preceding the Annual Session and Convention of the American College of Physicians and the American Medical Association, respectively. The closing date for registration for oral examinations is February 1, 1948.

The Board's next written examination will be on October 18, 1948, with a closing date for registration of June 1, 1948.

The American Board of Pediatrics, Inc., 718 Royal Union Bldg., Des Moines, Iowa; Lee F. Hill, M.D., Secretary-Treasurer. The next written examinations will take place on March 12, 1948. Oral examinations are scheduled for April 23–25, 1948, in Cleveland, Ohio; and for June 25–27, 1948, in Chicago, Ill.

The American Board of Physical Medicine, 30 N. Michigan Ave., Chicago 2, Ill.; Robert L. Bennett, M.D., Secretary-Treasurer. The next examination period will be two days prior to the Annual Convention of the American Medical Association, June, 1948, Chicago, Ill.

The Lois Grunow Memorial Clinic, Phoenix, Ariz., will present an instructional program February 19–21, 1948. The following will be among the contributors to the program. Francis D. Murphy, M.D., F.A.C.P., Professor and Head of the Department of Medicine, Marquette University; Lester W. Paul, M.D., F.A.C.R., Professor of Radiology, University of Wisconsin Medical School; Frank H. Lahey, M.D., F.A.C.S., Lahey Clinic, Boston, Mass.; Vincent J. O'Conor, M.D., F.A.C.S., Professor and Chairman of Department of Urology, Northwestern University Medical School; Elvira Goettsch, M.D., Assistant Professor of Pediatrics, University of Southern California; William H. Bickel, M.D., F.A.C.S., Section on Orthopedics, Mayo Clinic, Rochester, Minn.; and the following members of the Clinic staff: Henry G. Williams, M.D., F.A.C.S., Department of Surgery; Hugh Wilson, M.D., Department of Clinical Laboratory; Norton J. Wood, D.D.S., Department of Orthodontia; John Eisenbeiss, M.D., Department of Neurosurgery; O. W. Thoeny, M.D., F.A.C.S., Department of Eye, Ear, Nose and Throat.

Important Contribution to College Library

H. Sheridan Baketel, A.M., M.D., F.A.C.P., Director of the Reed & Carnick Institute for Medical Research, Jersey City, N. J., has presented to the College Library on behalf of the Institute the two volume *Opera Omnia* of Vesalius, the famous Boerhaave and Albini collection. This edition was published in Leyden in 1725 and contains plates and many engravings by Jan Wandelaer. This rare example of a medical classic has been described as follows:

First Collected Edition, a magnificent publication issued in commemoration of the 200th anniversary of the birth of Vesalius. The woodcuts of the Fabrica and of the Epitome are very beautifully copied and engraved on copper in the original size by Jan Wandelaer. The title-page is engraved after the edition of 1543. Oporinus' monogram, however, is omitted and the architecture slightly changed. The remaining wood engravings are copied entirely, with the additions, from the edition of 1555.

All the woodcuts of the Epitome are re-engraved, without exception. Vesalius' Epistola docens venan axillarem, etc., is omitted, also the Vesalian plates of 1538; on the other hand it contains De radice Chynae, Gabr. Fallopii observationes anatomicae (against Vesalius) and Vesalii anatomicarum G. Fallopii anatomicae examen (a rejoinder), and the posthumous Chirurgia magna in Vesalius' own handwriting which contains a number of small illustrations.—Fine, uncut copy; lacks plates 3, 74 and 75. —With the Edward C. Streeter bookplate.

The Eastern Pennsylvania Regional Meeting

The annual Eastern Pennsylvania Regional Meeting was held at the Warwick Hotel, Philadelphia, on November 21, 1947, under the Chairmanship of Dr. E. L. Bortz, College Governor for Eastern Pennsylvania. In addition to the Eastern Pennsylvanians, members from near-by New Jersey and Delaware were invited. In addition to an excellent scientific program, a reception and dinner were held in the evening at which the Officers and Regents of the College were in attendance as well as the deans of the various medical schools in Philadelphia, the President of the College of Physicians of Philadelphia, and of the Philadelphia County Medical Society. The attendance was gratifying, there being a total of 267 officially registered, of whom 193 were members of the College and 74 were guests.

Fellows and Associates of the American College of Physicians in South Carolina who were in attendance at the Post-Graduate Seminar of the Medical College of South Carolina, November 6, 1947, joined for a luncheon. College affairs were discussed at the luncheon, which was well attended.

The Omaha Mid-West Clinical Session, of which J. D. McCarthy, M.D., F.A.C.P., Omaha, College Governor for Nebraska, is a member of the Executive Committee, held its 1947 Session October 27–31. The meeting was a very successful one with a registration of 1,185. The program included as participants the following members of the College: F. Lowell Dunn, M.D., F.A.C.P., John F. Gardiner, M.D., F.A.C.P., Ernest Kelley, M.D., F.A.C.P., John R. Kleyla, M.D., F.A.C.P., Harold C. Lueth, M.D., F.A.C.P., Ernest L. MacQuiddy, M.D., F.A.C.P., Warren Thompson, M.D., F.A.C.P., Raymond L. Traynor, M.D., F.A.C.P., and J. Harry Murphy (Associate), all of Omaha. Guest speakers included Nelson W. Barker, M.D., F.A.C.P., Rochester, Minn.; Edward L. Bortz, M.D., F.A.C.P., Philadelphia; Franklin G. Ebaugh, M.D., F.A.C.P., Denver; Victor Johnson, M.D., F.A.C.P., Rochester, Minn.; Donald McCarthy, M.D., F.A.C.P., St. Paul; and Walter L. Palmer, M.D., F.A.C.P., Chicago.

Charles E. Kossmann, M.D., F.A.C.P., New York, N. Y., formerly Lieutenant Colonel, A.U.S., has been awarded the Legion of Merit for his accomplishment in the production of the "Flight Surgeon's Handbook," while Chief of the Department of Aviation Medicine of the Army Air Forces School of Aviation Medicine.

R. R. Snowden, M.D., F.A.C.P., College Governor for Western Pennsylvania, has been awarded the honorary degree of Doctor of Science by Washington and Jefferson College, Washington, Pa., at exercises held on November 1, 1947.

Oscar B. Hunter, M.D., F.A.C.P., Washington, D. C., has been elected to the position of President-Elect of the Southern Medical Association.

Alphonse McMahon, M.D., F.A.C.P., St. Louis, Mo., was elected to the position of President-Elect of the Mississippi Valley Medical Society at the November meeting of the Society's Board of Directors. Harold Swanberg, M.D., F.A.C.P., and Ralph McReynolds, M.D., F.A.C.P., both of Quincy, Ill., were elected Secretary-Treasurer and Account Officer. The next annual meeting of the Society will take place at Springfield, Ill., September 29–October 1, 1948, under the Presidency of Willard O. Thompson, M.D., F.A.C.P., Chicago, Ill.

To receive consideration for the 1948 annual essay prize of the Mississippi Valley Medical Society, essays must be submitted not later than May 1, 1948, to the Secretary of the Society. The prize of $100.00, a gold medal and a certificate of award is offered for the best unpublished essay on any subject of general medical interest and of practical value to the general practitioner of medicine.

The Fifty-eighth Annual Convention of the Association of the American Medical Colleges was held recently at Sun Valley, Idaho. Among the newly elected officers, Walter A. Bloedorn, M.D., F.A.C.P., Washington, D. C., was elected President; J. Roscoe Miller, M.D., F.A.C.P., Chicago, Ill., President-Elect; and Ward Darley, Jr., M.D., F.A.C.P., Denver, Colo., Member of the Executive Council.

George B. Dowling, M.D., F.A.C.P., Washington, formerly Captain in the U. S. Navy, has recently been appointed Deputy Administrator in the American Red Cross to assist Ross T. McIntire, M.D., F.A.C.P., who is directing that organization's program for the procurement and distribution of whole blood.

Andrew C. Ivy, M.D., Ph.D., F.A.C.P., Chicago, Vice President of the University of Illinois, delivered the Convocation address before the American College of Surgeons at New York City, September 12, 1947, on "Liberal Medical Education."

American College of Surgeons Presents Lecture Table and Lectern to the Royal College of Surgeons of England

On September 22, 1947, at Lincoln's Inn Fields, London, the American College of Surgeons formally presented to the Royal College of Surgeons of England a beautifully designed lecture table and a lectern "as a token of mutual friendship." At the same exercises, Honorary Fellowships were conferred by the Royal College of Surgeons of England on the following Officers and Regents of the American College of Surgeons: Arthur Wilburn Allen, Boston, President; Irvin Abell, Louisville, Chairman of the Board of Regents; Frank Howard Lahey, Boston, former President; Dallas Burton Phemister, Chicago, President Elect; Alfred Blalock, Baltimore, Regent. William Edward Gallie, Toronto, former President, was honored with the Honorary Gold Medal of the Royal College of Surgeons of England, "the most exclusive emblem of merit of the Royal College."

Evarts Ambrose Graham, St. Louis, former President of the American College of Surgeons, received from the Royal College the rare award of the Lister Medal.

The Honorary Medal of the Royal College of Surgeons of England was instituted in 1802. The leading considerations in awarding this medal are liberal acts or distinguished labors, researches, and discoveries, eminently conducive to the improvement of natural knowledge and of the healing art.

The Lister Award consists of a sum of £500, together with a bronze medal, awarded every three years, in recognition of distinguished contributions to surgical science, the recipient, who may be of any nationality, being required to give an address in London under the auspices of the Royal College of Surgeons.

The American Pharmaceutical Manufacturers' Association presented its distinguished award for 1947 to the American Medical Association at a meeting in New York on December 16. The award is made on nomination by a Scientific Advisory Committee which includes among its members David P. Barr, M.D., F.A.C.P., New York, Past President of the College; Anton J. Carlson, M.D., M.A.C.P., Chicago, Ill.; H. C. Hinshaw, M.D., F.A.C.P., Rochester, Minn.; Chester S. Keefer, M.D., F.A.C.P., Boston; John B. Youmans, M.D., F.A.C.P., Chicago. The award recognizes fundamental contributions in medical science to the public health as well as progress in basic research in drug therapy. The award was presented by Dr. Perrin H. Long of Baltimore in behalf of the A.P.M.A. and was accepted for the American Medical Association by its President-Elect, Roscoe L. Sensenich, M.D., F.A.C.P., South Bend, Ind.

Dr. Walter O. Klingman, F.A.C.P., recently accepted an appointment as Associate Professor of Neuropsychiatry in the University of Virginia's School of Medicine. He was formerly connected with the Neurological Institute of New York.

Charles E. Lyght, M.D., F.A.C.P., who has been Director of Health Education with the National Tuberculosis Association of New York City for the past five years, joined the staff of the Medical Division of Merck & Co., Inc., Rahway, N. J., December 1, 1947.

ELECTIONS TO MEMBERSHIP—THE AMERICAN COLLEGE OF PHYSICIANS

Philadelphia, Pa., November 23, 1947

(Lower case indicates Associates; FULL CAPITALS INDICATE FELLOWS)

Abel, Oliver, Jr., St. Louis, Mo.
ABERNETHY, THEODORE JUDSON, Washington, D. C.
Ailts, Bernard Henry, Wood, Wis. (V.A.)
ALPERS, BERNARD JACOB, Philadelphia, Pa.
AMTMAN, LEO, Chicago, Ill.
Angell, Rudolph, Rochester, N. Y.
Arbuse, David Irving, New York, N. Y.
ARNDAL, OTTO, Glendale, Calif.
Atlas, Donald Herman, Evanston, Ill.

BABEY, ANDREW MICHAEL, Brooklyn, N. Y.
BARRIER, CHARLES WESLEY, Ft. Worth, Tex.
BARTHOLOMEW, RAYMOND KENNETH, Dayton, Ohio
BEARD, EDMUND EARL, Cleveland, Ohio
BECK, DAVID, New York, N. Y.
Berger, Herbert, Staten Island, N. Y.
BLAIN, DANIEL, Washington, D. C. (V.A.)
Blalock, Tully Talbot, Atlanta, Ga.

BLISS, RAYMOND WHITCOMB, (MC), USA
Boyer, Paul Kenneth, Summit, N. J.
Brandt, Charles Richard, Mechanicsburg, Pa.
Braunstein, John Rutley, Cincinnati, Ohio
Breuhaus, Herbert Charles, Chicago, Ill.
Brookens, Norris L., Urbana, Ill.
Brussel, James Arnold, Willard, N. Y.
Bucholz, Donald John, Omaha, Nebr.
BURNEY, LEROY EDGAR, Indianapolis, Ind.

Calvy, George Lloyd, (MC), USN
Cammerer, Herbert Richard, Dayton, Ohio
CARDON, LEONARD, Chicago, Ill.
Carroll, Francis Brian, Waban, Mass.
Charr, Robert, Philadelphia, Pa.
Chester, Edward Milton, Berea, Ohio
Clark, Arthur Paul Carman, Calgary, Alta, Can.
Cochran, William Lloyd, Ann Arbor, Mich.
Cohen, Stanley, New Orleans, La.
Cole, Seymour Lewy, Los Angeles, Calif.
Coleman, Francis Carter, Des Moines, Iowa
CONNOLLY, ALOYSIUS JOHN BERCHMANS, Washington, D. C.
COOMBS, FREDERICK STANLEY, JR., Youngstown, Ohio
Cooper, Talbert, Rochester, Minn.
Correll, Howard Leroy, Milwaukee, Wis.
Cosby, Richard Sheridan, Pasadena, Calif.
CRAMER, CHARLES, Jackson Heights, N. Y.
Crampton, Joseph Hamilton, Seattle, Wash.
Creel, Wylie Fackler, Austin, Tex.
Curtis, Harold Goldsmith, Cleveland, Ohio
Curtis, Raleigh Robert, Temple, Tex.
Cutter, Edward Parker, Clarksville, Tenn.

Dale, Mark, Detroit, Mich.
DANIELS, EINAR ROBERT, Milwaukee, Wis.
Danstrom, John Richard, Oklahoma City, Okla.
DARNALL, CHARLES MILTON, Austin, Tex.
Davis, C(lare) Nelson, Philadelphia, Pa.
Dear, Richard Hamilton Bryarlie, (MC), USA
DeFEO, HERMAN FELIX, Chicago, Ill.
Del Vecchio, James John, Wheeling, W. Va.
Denman, William Emmett, Jr., Memphis, Tenn.
Dennison, Alfred Dudley, Jr., Maplewood, N. J.
Doerner, Alexander Andrew, USPHS
DOLKART, RALPH ELSON, Chicago, Ill.
Dumanis, Abraham Aaron, Flushing, N. Y.
Dunbar, William, Philadelphia, Pa.

Eagan, John Charles, Los Angeles, Calif.
Erdmann, Albert John, Jr., New York, N. Y.
ERICKSON, ELDON WESLEY, Detroit, Mich.
Erwin, Herbert Jones, St. Louis, Mo.

FAHR, GEORGE EDMESTON, Minneapolis, Minn.
Fanson, Anna Ethel, Pasadena, Calif.
FARQUHARSON, RAY FLETCHER, Toronto, Ont., Can.
Feder, Aaron, Jackson Heights, N. Y.
FINKELSTEIN, DAVID, Philadelphia, Pa.
Flance, Israel Jerome, St. Louis, Mo.
Flannery, Wilbur Eugene, New Castle, Pa.
Fleming, J(acob) Will(iam), Jr., Moberly, Mo.
FLEMING, RALPH GIBSON, Durham, N. C.
Friedland, Carl Kampton, Philadelphia, Pa.
FRIST, THOMAS FEARN, Nashville, Tenn.
FULGHUM, CHARLES BENNETT, SR., Milledgeville, Ga.
Fusting, William Hammond, Baltimore, Md.

Gambill, William Dudley, Indianapolis, Ind.
Garvin, Robert Odell, Pittsburgh, Pa.
GELBACH, PHILIP DELMONT, Detroit, Mich.
Gemmell, John Patmore, Winnipeg, Man., Can.
GILMOUR, MONROE TAYLOR, Charlotte, N. C.
Golding, Frank Cunningham, El Paso, Tex.
GOMPERTZ, JOHN LANGDON, Oakland, Calif.
Goodman, Joseph Irving, Shaker Heights, Ohio
Gootnick, Abraham, Memphis, Tenn. (V.A.)
GOULEY, BENJAMIN ALEXIS, Philadelphia, Pa.
GREEN, MAYER ALBERT, Pittsburgh, Pa.
Greenfield, Herbert, Newark, N. J.
Greenwald, Louis, New York, N. Y.
Grishman, Arthur, New York, N. Y.

Harris, Richard Lamar, Los Angeles, Calif. (V.A.)
Harrison, Francis French, Cooperstown, N. Y.
HARTWELL, ALFRED STEDMAN, Honolulu, T. H.
HASSETT, F(LORENCE) SULLIVAN, Elmira, N. Y.
Hatton, Don Virgil, Huntington, W. Va.
Hauenstein, Virgil Dee, Cincinnati, Ohio
Hause, Welland Angel, (MC), USA
Hay, William Edwin, Denver, Colo.
HAYES, PAUL, (MC), USA
HEDGES, ROBERT NATHANIEL, Chicago, Ill.
Henderson, Allison Burney, Detroit, Mich.
Henry, J(ennings) Lamont, Atlanta, Ga.
HERNDON, JAMES HENRY, Dallas, Tex.
Herzog, Robert Simon, Chicago, Ill.
HILDEBRAND, ALICE GRACE, Seattle, Wash.
Hiles, Charles Hall, Wheeling, W. Va.
Hill, Alfred Humphrey, San Antonio, Tex.
Hock, Charles William, Augusta, Ga.
HOFFMAN, BYRON JAY, Atlanta, Ga.
Holley, Howard Lamar, Birmingham, Ala.
Holmes, Joseph Henry, Denver, Colo.
Hortenstine, John Campbell, Winchester, Va.
Howell, Thomas Wellington, Newark, N. J.
Hubbs, Roy Sears, Palo Alto, Calif. (V.A.)
HUMPHREY, ARTHUR ALLAN, Battle Creek, Mich.

ISRAEL, HAROLD LOUIS, Philadelphia, Pa.
Izenstein, Louis Arthur, Springfield, Mass.

Jarrett, Thirl Edwin, (MC), USN
Jarvis, James Armstead, Kansas City, Mo.
Jastremski, Bruno, (MC), USA
Johnson, Chester Earle, Jr., Tuscaloosa, Ala.
Johnson, John Beauregard, Washington, D. C.
JOHNSON, SCOTT, New York, N. Y.
JONES, EDGAR, Nashville, Tenn.

KAPLAN, BERNARD IRVING, Ossining, N. Y.
Karl, Michael Meyer, St. Louis, Mo.
Kemble, Edward Ernest, Erie, Pa.
Kimball, Stanley, Dedham, Mass.
Kindschi, Leslie George, Monroe, Wis.
Kirshen, Martin Moses, Chicago, Ill.
KIRSNER, JOSEPH BARNETT, Chicago, Ill.
KIPSTEIN, MELVIN BYRON, St. Louis, Mo.
KLOSK, EMANUEL, Newark, N. J.
KOSSMANN, CHARLES EDWARD, New York, N. Y.
Krinsky, Charles Morris, New London, Conn.
Kutzer, Max, Syracuse, N. Y.

Lamberta, Frank, Jamaica, N. Y.
Lang, Valorus Frederick, Milwaukee, Wis.
Latimer, John Wilmer, Jr., Washington, D. C.
Lawler, Edmund Griffin, Chicago, Ill.
LEAVELL, BYRD STUART, Charlottesville, Va.
Levy, Harold, Brooklyn, N. Y.
Levy, Louis, II, New Orleans, La.
Levy, Marvin Shephard, Beverly Hills, Calif.
Lieberson, Abraham, New York, N. Y.
LINN, GEORGE CHARLES, New York, N. Y.
Lipsitz, Morton Hirsch, Buffalo, N. Y.
LIPTON, HARRY ROBERT, Atlanta, Ga.
LITTERAL, EMMETT BRYAN, (MC), USA
LITWINS, JOSEPH, New York, N. Y.
LUCIA, SALVATORE PABLO, San Francisco, Calif.

Maimon, Samuel Newman, Dayton, Ohio
Mansfield, James Scott, Boston, Mass.
Manulis, Fred(erick) Everett, Palm Beach, Fla.
Marshall, Frank Anton, Weehawken, N. J.
Mason, Eugene Edgar, Dallas, Tex.
McCaffrey, Maurice Henry, Pittsburgh, Pa.
McCollum, Wiley Thomas, Oklahoma City, Okla.
McConahay, Harold Arthur, Holdrege, Nebr.
MENEFEE, ELIJAH EUGENE, JR., Durham, N. C.
MERKLE, CLARENCE EDWARD, Alton, Ill.
Merrick, Benjamin August, Dallas, Tex.
MINISH, LAWRENCE T., JR., Louisville, Ky.
MIRSKY, I(SADORE) ARTHUR, Cincinnati, Ohio
MITCHELL, ROBERT HARTWELL, Ft. Worth, Tex.

Moe, Allan Eugene, Fargo, N. D.
MOENCH, LOUIS GARDNER, Salt Lake City, Utah
MOLONEY, WILLIAM CURRY, Boston, Mass.
MONACO, THOMAS CLIFFORD, Jamaica, N. Y.
MONTO, RAYMOND WALTER, Detroit, Mich.
Morgan, Allan Vincent, Pittsburgh, Pa.
Moseley, Vince, Charleston, S. C.
Murphy, Albert Vincent, Omaha, Nebr.

Naide, Meyer, Philadelphia, Pa.
Nevin, Robert John, Washington, Pa.
Nichols, Ralph Gibbs, Knoxville, Tenn.
NORMAN, JAMES KINDRED, Ft. Worth, Tex.
Notier, Victor Anthony, Grand Rapids, Mich.
Numainville, Leon Joseph (MC), USA
Nyiri, William, Newark, N. J.

OCHS, LOUIS, JR., New Orleans, La.
OHLER, W(ILLIAM) RICHARD, Jamaica Plain, Mass.
Oxman, Albert Charles, Denver, Colo.
Ozarin, Lucy Deborah, Buffalo, N. Y. (V.A.)

PACKARD, EDWARD NEWMAN, Trudeau, N. Y.
Parker, Ralph Chandler, Jr., (MC), USN
Partch, Wallace Taylor, Oakland, Calif.
PAULL, ROSS, La Jolla, Calif.
PELLICANO, VICTOR LOUIS, Niagara Falls, N. Y.
PERRY, T(HORNTON) TAYLOE, III, Washington, D. C.
Petersen, Drew Mathew, Ogden, Utah
PFEIFFER, MILDRED CLARA JULIA, Merion Station, Pa.
Plessinger, Virgil Allen, Cincinnati, Ohio
PORTER, RENO RUSSELL, Richmond, Va.
Post, John, Chicago, Ill.
PRIDDLE, WILLIAM WELMORE, Toronto, Ont., Can.
Proudfit, William Lyle, Cleveland, Ohio

Radke, Ryle August, (MC), USA
Rafferty, Theodore Newell, New Orleans, La. (V.A.)
Rand, Harold, Miami, Fla.
RANGES, HILMERT ALBERT, New Rochelle, N. Y.
Rappaport, Henry, Washington, D. C. (V.A.)
RAY, EDWARD SCOTT, Richmond, Va.
REDISH, JULES, Lynbrook, N. Y.
REIN, GERALD NORMAN, Benton Harbor, Mich.
Rieber, Charles Wolfe, Forest Hills, N. Y.
Rifkin, Harold, New York, N. Y.
ROBERTS, JOSEPH THOMAS, Washington, D. C.
Rosenblatt, William, Wichita Falls, Tex.
Rosenthal, Sydney, Newark, N. J.
Ross, John Richard, Milton, Mass.
Rudnikoff, Isadore, Yonkers, N. Y.
Rumball, John Marcus, Coral Gables, Fla. (V.A.)
Ryan, Raymond Charles, Jamaica, N. Y.

Sackey, Maurice Seville, Philadelphia, Pa.
SAUER, WILLIAM GEORGE, Rochester, Minn.
Scanlan, William Dennis, Jr., Brooklyn, N. Y.
SCHEIFLEY, CHARLES HOLLAND, Rochester, Minn.
SCHERLIS, SIDNEY, Baltimore, Md.
Schlachman, Milton, Corona, N. Y.
SCHNEIERSON, S(OL) STANLEY, New York, N. Y.
SCHUCK, CARL ALFRED, Hamilton, Ohio
SCHWEMLEIN, GEORGE XANTHIAN, Cincinnati, Ohio
Sears, William Norman, Palo Alto, Calif.
SEYBOLD, EDWARD GEORGE, Toledo, Ohio
Shafer, Harold Camden, Bay City, Mich.
Shafer, June Carol, New York, N. Y.
SHAY, HARRY, Philadelphia, Pa.
Shechter, Fred Ralph, Philadelphia, Pa.
SHILLITO, FREDERICK HOPKINS, New York, N. Y.
Siglin, Irvin Sidney, Chicago, Ill.
Silver, Aaron, New York, N. Y.
Simkins, Samuel, Philadelphia, Pa.
Simmons, Eugene Earl, Omaha, Nebr.
Skubi, Kazimer Bogar, Seattle, Wash.
Sloan, Fred Ries, (MC), USA
Smith, John Goodrich, Rocky Mount, N. C.
Soderstrom, Kenneth Malcolm, Seattle, Wash.
SOKOLOV, RAYMOND A., Detroit, Mich.
Spencer, Gerald Arthur, New York, N. Y.
STARRS, ROBERT ALPHONSUS, Ottawa, Ont., Can.
Sterne, Eugene Herman, Jr., Cincinnati, Ohio
Steward, Williams Dean, Orlando, Fla.
STEWART, SLOAN GIFFIN, Atlantic City, N. J.
Stine, Leonard Alvin, Chicago, Ill.
Strauss, Victor, Cincinnati, Ohio
Stroebel, Charles Frederick, Jr., Rochester, Minn.
Stuckey, Charles LeGrand, Charlotte, N. C.
Styron, Charles Woodrow, Raleigh, N. C.
Sweet, Herbert Chittenden, Affton, Mo.
SWEIGERT, CHARLES FRANCIS, San Francisco, Calif.

Taubenhaus, Matthew, Chicago, Ill.
TAYLOR, JAMES SHERWOOD, (MC), USA
TAYLOR, LESTER, Cleveland, Ohio
TAYLOR, ROBERT DEWEY, Cleveland, Ohio
Thal, William S., Toledo, Ohio
Thompson, George Newton, Los Angeles, Calif.
Thompson, Joseph James, Gloversville, N. Y.
Tierney, Gerald Miles, (MC), USA
Tierney, Nicholas Archibald, Miami Beach, Fla.
TOWNSEND, STUART ROSS, Montreal, Que., Can.
Toy, Calvert Rogers, New Brunswick, N. J.
Tredway, John Buffington, Erie, Pa.

UHR, NATHANIEL, Topeka, Kans. (V.A.)
Underwood, Franklin Judson, Portland, Ore.

VOORHIES, NORTON WILLIAM, New Orleans, La.

Ward, George Joseph, Poughkeepsie, N. Y.
Warren, Irving Aaron, Detroit, Mich.
Wasserman, Louis Robert, New York, N. Y.
Watson, (Ruth) Janet, Brooklyn, N. Y.
Watts, Frederick Beemer, Grosse Pointe Woods, Mich.
Weaver, Myron McDonald, Minneapolis, Minn.
Webster, John Joseph, New York, N. Y.
Weeks, Kenneth Durham, Rocky Mount, N. C.
WENDKOS, MARTIN HOWARD, Philadelphia, Pa.
WHITE, BENJAMIN VROOM, Hartford, Conn.
Wilcox, Abbott Yates, Jr., Cincinnati, Ohio
Wilder, Russell Morse, Jr., Minneapolis, Minn.
Wilkerson, Hugh Lyon Clements, USPHS
WILLIAMS, ROBERT HARDIN, Newton Lower Falls, Mass.
Willis, James Garnett, Fredericksburg, Va.
WILNER, PAUL ROBERT, Washington, D. C.
Wilson, Keith Singleton, St. Louis, Mo.
WILSON, W(ALTER) HOWARD, Raleigh, N. C.
WINSOR, TRAVIS WALTER, Los Angeles, Calif.
Wise, Robert Allen, Temple, Tex. (V.A.)
WOLFRAM, DONALD J., Indianapolis, Ind.
Wolfson, Samuel Abraham, Los Angeles, Calif.
WOSIKA, PAUL HENRY, Chicago, Ill.
WRIGHT, ROBERT BROY, Baltimore, Md.

Young, Bascom Brockenbrough, Wingdale, N. Y.
Young, Dennison, New York, N. Y.
Young, John David, Jr., Memphis, Tenn.
Younge, Walter Archibald, St. Louis, Mo.
Youngman, Robert Armstrong, Lincoln, Nebr.

ZAVOD, WILLIAM ABRAHAM, Mount Vernon, N. Y.
Zieman, Alphonse Hays, Mobile, Ala.

ERNEST BRENNAN BRADLEY

OBITUARY

DR. ERNEST BRENNAN BRADLEY

Ernest Brennan Bradley, A.B., M.D., M.A.C.P., Lexington, Ky., died November 12, 1947, after a long illness from an extensive encephalopathy associated with several circulatory episodes, involving the brain and heart.

Dr. Bradley was born May 16, 1877, at Lexington, Ky. He received his A.B. degree from Transylvania College in 1895; his medical degree from the University of Michigan Medical School in 1904. Interned at the New York City Hospital, Welfare Island; City Bacteriologist, Lexington, 1908–25; Health Officer, Fayette County, 1909–24; Chairman, Fayette County Board of Health, 1924–38; Member, Lexington City Board of Health, 1932–38; Chairman, combined Fayette County and Lexington City Board of Health, 1938—; Member, the Lexington Clinic, 1920—; Visiting Physician, St. Joseph's Hospital (since 1907) and Good Samaritan Hospital (since 1909); Member, Medical Advisory Board, Julius Marks Sanatorium; former President, Fayette County Medical Society and Kentucky Midland Medical Society; Member, Kentucky State Medical Association, Mississippi Valley Medical Association and American Medical Association; former Secretary and former Chairman of the Section on Medicine, Southern Medical Association; Councillor, American Clinical and Climatological Association; served during World War I as Major, Medical Corps, U. S. Army; Diplomate, American Board of Internal Medicine.

Dr. Bradley became a Fellow of the American College of Physicians in 1919, and served on the Board of Governors from 1925 until 1935, being Vice Chairman from 1930 to 1933 and Chairman, 1934–35. In 1935 he was selected as President-Elect as an outstanding example of an accomplished, outstanding internist without academic appointments. He served as President, 1936–37, and thereafter remained on the Board of Regents until 1940. He served on the Committee on Credentials from 1930 to 1940; on the Executive Committee, 1935–37; on the Committee on Public Relations, 1934–36; on the Consulting Committee on Annual Sessions, 1936–39; on the Committee on Future Policy for the Development of Internal Medicine, 1938–39; and on the Committee on Nominations, 1940–41.

Dr. Bradley's first important contribution was the development of a more extended and deeper interest on the part of members of the Board of Governors through his advocacy of a greater recognition and extension of the duties and authority of that Board. He was one of the early Governors who organized sectional meetings of members within his territory, and who promoted this activity among other Governors. One of his greatest contributions to the College was his work as a member of the Committee on Credentials, through disseminating a better understanding of the admission standards of the College among the several Governors and the clarification and rationalizing of admission regulations. The choice of Dr. Bradley as President was an indication that this College shall recognize outstanding practitioners of Internal Medicine, and that the Presidency shall not always be awarded to teachers, research workers and pure scholars—a recognition which met with wide approval among the Fellows. Shortly after his induction to the Presidency, the College moved into its present permanent home in Philadelphia. Also, during the early part of his Presidency, the American Board of Internal Medicine was established.

Further contributions made by Dr. Bradley during his Presidency, included: an appropriation of $1,000.00 for the aid of the National Conference on Nomenclature of Disease; the establishment of a second Research Fellowship; a closer relationship between the Regents and Governors through the initiation of a joint dinner-meeting of the two Boards preceding the opening of each Annual Session; the establishment of the policy that the College membership should not be restricted wholly to Internal

Medicine, but should include the allied specialties; the establishment of a liaison committee to confer with the American College of Surgeons concerning matters of mutual interest; an amendment to the By-Laws providing for Alternate Governors for attendance at the Annual Sessions; the establishment of Roundtable and Panel Discussions on the Annual Session Programs; adoption of a proposal to prepare a History of the American College of Physicians, with appointment of Dr. William Gerry Morgan, M.A.C.P., as Historian.

At the 1947 Convocation at Chicago on April 30, a Mastership was conferred upon Dr. Bradley in recognition of his eminent career and his outstanding contributions to the College.

Although not unexpected, his death came as a great shock to his numerous friends, both in and out of the medical profession, but particularly in the American College of Physicians. His accomplishments richly entitled him to his many honors, but his warm handshake, his cheerful smile and manner, his sincerity and loyalty will longer be remembered and cherished even more than his achievements. New acquaintances soon became his devoted friends. Probably no one individual in the College made such a large number of loyal friends who loved him for his own delightful style of wit and humor, his companionship and his sound ideas for the betterment of the College.

It should be mentioned also that his great popularity was shared by his wife, Norma, who accompanied him on most of his trips to College meetings, encouraging him to the utmost in every way. Indeed, so much were they a part of one another that one usually heard not the name, Ernest, alone, but "Ernest and Norma." With Mr. Loveland, the Executive Secretary, and Mrs. Dowden, it was our sad privilege to visit Ernest only two days before his death. Even then, in his disorientation that so often precedes such passings, with his infectious cheerful smile, and recognizing all of us, he immediately began planning for our trip (this time by plane) to the College meeting in San Francisco. Shortly after he sank into his final sleep with a smile on his face, and passed on to his well deserved reward, without apparent suffering. He is gone, and those who had the great good fortune to know him (and "to know him was to love him") became better men and women for such a friendship. His creed is so well stated in the following verse by Van Dyke, entitled

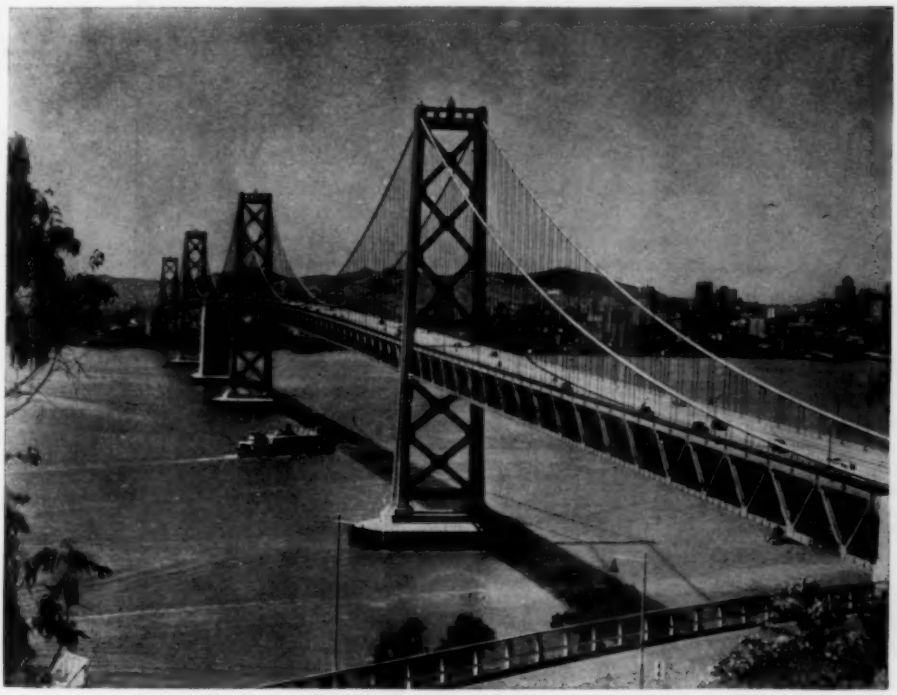
FOUR THINGS

Four things man must learn to do,
If he would make his record true,
To think without confusion clearly,
To act from honest motives purely,
To trust in God and Heaven securely.

—C. W. Dowden, M.D., F.A.C.P.,
Governor for Kentucky

SAN FRANCISCO: SCENIC CITY AND MEDICAL CENTER A.C.P. MEETING PLACE APRIL 19–23, 1948

"California, here we come!" This slogan of the Argonauts of the "gold rush" days is today, approximately one hundred years later, changed to "San Francisco, here we come!" The occasion of the present slogan is due to two simultaneous events: the Twenty-ninth Annual Session of the American College of Physicians, and the Centenary of the Discovery of Gold. Many descendants of those pioneers who came for gold will come this year not for gold as a yellow metal, but to behold the miracle wrought by time in California, and to seek the easily uncovered "pearls of wisdom" which lure Fellows and Associates to the annual meetings of the American College of Physicians.



The San Francisco-Oakland Bay Bridge.

San Francisco is located on a peninsula six by seven miles in area, and looks down on a landlocked harbor 453 square miles in extent. The charm of the city and its surroundings is well known, but it will not be amiss to mention briefly some of its important historical features.

Mission Dolores—The church where San Francisco was born.

The old Mission Dolores stands at Mission and Sixteenth Streets. Once considered "out in the country," it is now in the heart of the city. Founded by the Padres in the eventful year of 1776, the mission was actually built by Indians who baked the soil into adobe bricks and fastened the beams together with wet rawhide thongs. It has been restored as need has arisen, and is open to visitors.

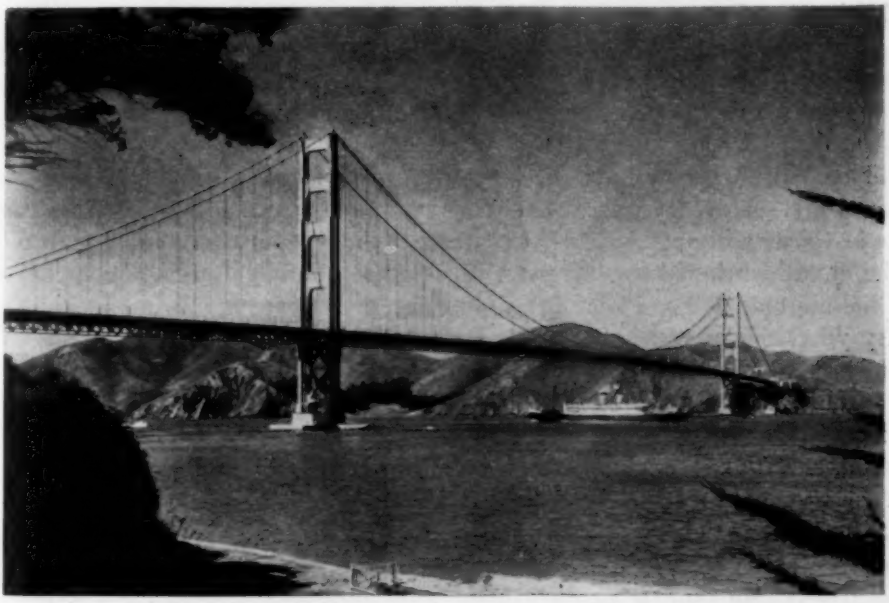
The Presidio of San Francisco, now occupied by the United States Army, was once the fort and the home of the Spaniards. In 1769 they discovered the Golden Gate and its magnificent bay, adding California to the Province of Mexico. This area was administered by a governor sent from Mexico. General Vallejo, the last of the Mexican governors, is honored and remembered by Californians today.

It was at the Presidio that the Russian, Nikolai Petrovich de Rezanov, courted and won the beautiful Doña Maria Conception Arguello, daughter of the Commandante. Rezanov perished on his long journey back to Moscow, and so was never able to claim his bride or build the coastal trading center of which he had dreamed. In grief over the loss of her lover, Doña Concha

joined a holy order, and, as Sister Dominica, was finally laid to rest at Mission Dolores.

Just two blocks from Union Square and an equal distance from the financial district is Chinatown with its century old exemplification of the culture of the Orient. Its many shops and Chinese restaurants are part of the itinerary of nearly all travelers to San Francisco. This is the largest Chinese community outside of China.

In the earlier years of the city the coming and going of ships was one of the main outside interests of San Franciscans. Vessels from all over the world, China, Japan, India, New York, came with immigrants and goods for trade. Today when one visits the Embarcadero to see the cargoes that come and go, gold is not in evidence as it was in '49, but wealth and the atmosphere of far and distant places still accompany the vessels that slip into the harbor through the Golden Gate, passing under the Golden Gate Bridge, the longest and tallest single-span suspension bridge in the world. From the Embarcadero one can view the San Francisco-Oakland Bay Bridge, which stands without a rival as to length, the total span being eight and one quarter miles.



A ship passing under the Golden Gate Bridge on its way out the Golden Gate into the Pacific.

Just beyond the Embarcadero is Fisherman's wharf. Here the fishing craft swing at anchor while the day's catch is unloaded. Shrimp and crayfish are cooked in large kettles in front of the many restaurants on the wharf. The well filled tables inside attest the psychological advantage of this form of advertising fresh sea food. As you leave Fisherman's wharf and arrive at the foot of Powell Street, you will find one of the historic cable cars being

Cliff House with the seals disporting themselves on the rocks only a few hundred yards from shore.

California street cable car climbing one of San Francisco's hills.

spun around on a turntable in preparation for its return trip through the heart of the city. While the car clang-clangs up the hills you will cling to your seat. On top of Nob Hill a beautiful view of the harbor and bay unfolds itself and one forgets the uneasiness of the perpendicular ascent.

There remains still our Golden Gate Park, an important feature of San Francisco that all visitors will want to see. This area was once barren sand dunes stretching between the city and the ocean. In 1873, The Santa Clara "Democrat" wrote, "Of all the white elephants the city of San Francisco ever owned, they now have the largest and heaviest in the shape of 'Golden Gate Park'—a dreary waste of shifting sand hills where a blade of grass cannot be raised without four posts to support it and keep it from blowing away." The dunes continued to shift until 1887, when John McLaren, a Scotchman of indomitable will and keen foresight, was put in charge. In his more than fifty years of service, "Uncle John" planted more than a million trees and made the barren dunes into one of the world's most beautiful parks.

California is about to celebrate three centennial years: 1948, the Gold Discovery; 1949, the Gold Rush; and 1950, Statehood. January 24th, 1948, marks exactly one hundred years since James W. Marshall discovered gold at Sutter's new sawmill at Coloma on the American River. On this day Californians, led by Governor Earl Warren, will hold a ceremony at the James Marshall gold discovery site at Coloma. It is planned to introduce features reminiscent of the days of the gold discovery in connection with the coming meeting of the American College of Physicians, April 19 to 23.

For the past fifty years or more, San Francisco may be said to have enjoyed a uniform acceleration in the medical fields of research, teaching, and hospital services, due to expanding opportunities for development of medical education and public health. The past thirty-five years in particular have been fruitful in research at the Stanford University School of Medicine, the Hooper Foundation for Medical Research, and the University of California. The latter institution has more recently gained world-wide recognition

through the elaboration of the cyclotron by Ernest Lawrence of the Physics Department in Berkeley, California. This gave impetus to the study of nuclear physics and resulted in the production of radioactive compounds for use in research and the treatment of disease, both in Berkeley and at the University of California Medical School in San Francisco. The Biophysics Department has provided isotopes for intensive investigation of disease in the domain of animal and plant life, thus opening up fields of research undreamed of a half century ago.

Lane and Stanford University Hospitals.

Lane Medical Library, Stanford University School of Medicine.

San Francisco has two class A medical schools: Stanford University School of Medicine and the University of California Medical School.

The Medical Department of the University of the Pacific was the first medical college on the Pacific Coast. Founded by Elias Samuel Cooper in San Francisco in 1858, it was discontinued in 1864, reorganized six years

later, and affiliated with University College in 1872 under the name of the Medical College of the Pacific. These colleges were succeeded in 1882 by Cooper Medical College, incorporated by Dr. Levi Cooper Lane and named in honor of his uncle, Dr. Elias Samuel Cooper.

In 1882 Dr. Lane built the first of the present college buildings in San Francisco, on land donated by himself. Further gifts of Dr. Lane include Lane Hospital (1894), the Lane Medical Lectureship (1896), and provision for a library building.

Under permission granted by Dr. Lane, the Cooper Medical College was transferred to Leland Stanford Junior University in 1908. The main buildings in San Francisco consist of the Clinical and Laboratory Building, the Ruth Lucie Stern Research Laboratory, Lane Hospital with a capacity of 180 beds, and the Stanford University Hospital with about 130 beds. The Lane Medical Library is housed in a separate building erected in 1912, opposite the Clinical and Laboratory Building. This is the largest medical library west of Chicago and contains over 108,000 volumes. It has become a center for library service throughout the entire Pacific Coast region.

The laboratories of Anatomy, Bacteriology and Experimental Pathology, Chemistry and Physiology are located on the Campus at Stanford University, thirty miles southeast of San Francisco, adjoining the city of Palo Alto.

The entering class in the Medical School is limited to sixty students. The course is four years but all students are required to take a fifth year (interne year) before receiving the degree of Doctor of Medicine. The School of Medicine, in coöperation with the San Francisco Department of Health, controls about 500 beds in the San Francisco Hospital.

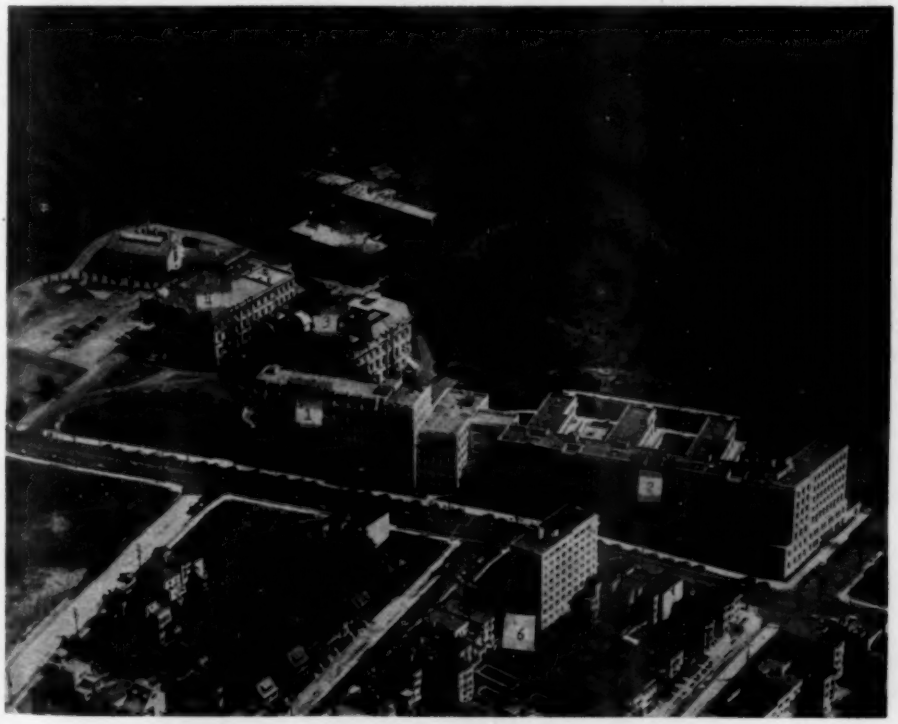
The history of the development of the University of California Medical School had its inception in 1864 when Dr. H. H. Toland erected a building in San Francisco to serve as a center for a medical school. In 1873 this building, then known as Toland Hall, was transferred to the Regents as a department of the University of California. The medical faculty controlled the policy of the school, and its support was derived from fees collected from the students. In 1898 the school was moved to its present situation on Parnassus Heights, where the late Adolph Sutro had given thirteen and one-half acres of land to the University. The Regents, in 1902, passed a resolution which made the Medical Department an integral part of the University. The properties of the school were transferred to the University of California and full support of the school was assumed by the Regents. Suitable laboratories were equipped and the first two years of medicine were put on an academic basis. The earthquake and fire of 1906 destroyed the Out-patient Department, necessitating transfer of the work of the first two years to Berkeley. The main building of the school was changed into a hospital and out-patient clinic.

In 1915 an affiliation was made with the Hospital for Children and Training School for Nurses, and in the same year elective courses in Homeopathic Therapeutics were included in the curriculum.

The present University of California Hospital was completed in 1917; two years later a Nurses' Home was erected across Parnassus Avenue from the hospital. In 1933 a new out-patient building attached to the hospital was opened; in 1928 laboratories for the teaching of Bacteriology and Pharmacology were provided on the San Francisco Campus. At Berkeley the divisions of Anatomy, Biochemistry and Physiology are housed in the Life Sciences Building, which was completed in 1930.

Plans are completed and the funds provided by the State Legislature for a new University Hospital and a Medical Sciences Building, which will be erected at the Medical Center in San Francisco in the near future.

The Langley Porter Clinic, a part of the Department of Institutions of the State of California, was opened in 1942. Situated at the Medical Center, this building is a 100-bed research and teaching institute for psychiatry, erected by the Department of Mental Hygiene of the State of California with the provision that the research and teaching functions of the Hospital shall be carried on under the direction of the University of California Medical School. The clinic includes an operating room, x-ray laboratory, a laboratory for electroencephalography, and an occupational therapy department.



Airplane view of The University of California Medical Center.

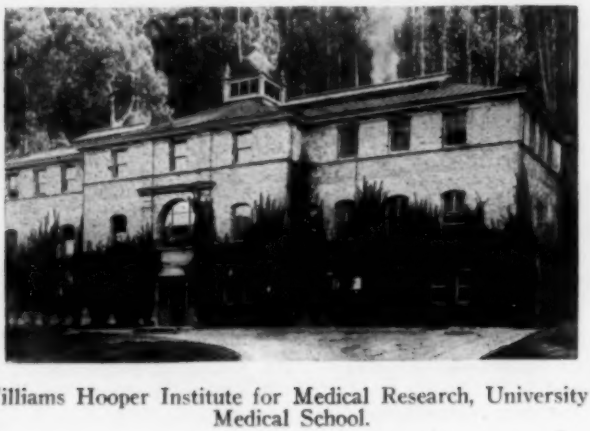
1. New Out-patient Department Building.
2. University Hospital.
3. Laboratories Building (Preclinical Departments).
4. School of Pharmacy.
5. Hooper Institute for Medical Research.
6. Nurses' Home.

Through the generosity of the Commonwealth Fund of New York City, a child guidance clinic and studies in child psychiatry were instituted.

The University Hospital has a capacity of more than 300 beds. It is essentially for teaching and, through support from the State of California and from endowment funds, a certain number of free beds are available. Such patients come from various parts of California and the Pacific Coast. The San Francisco Hospital is a municipal hospital built in 1915 at a cost of $3,500,000, operated by the Board of Health of the City and County of San Francisco for citizens unable to pay for hospital care. There is a main group of 21 occupied wards, a Tuberculosis Department of twelve occupied wards and an Isolation Department of four wards. About 380 beds in the main group and 200 beds in the Tuberculosis Department are assigned to the University of California Medical School. The Psychopathic Department is equipped to care for 100 patients, and the Maternity Department cares for 125 patients. These services are divided between the two University medical schools, Stanford and California.

The Laguna Honda Home is an adjunct of the San Francisco Hospital. It houses approximately 1,900 persons, 800 of whom are confined to the infirmary provided for the care of the aged and chronically ill. The infirmary is a modern hospital with nineteen wards. It has an excellently equipped surgery, x-ray department, laboratory and morgue. A small outpatient clinic is provided for ambulatory cases. The University of California Medical School supervises the medical care of the patients in return for teaching and clinic privileges.

In January, 1947, the Laboratory of Experimental Oncology was established as a coöperative project in connection with cancer research. This laboratory is housed in the Laguna Honda Home and contains electrophysiologic equipment for the study of physiology in cancer patients, a biochemical-immunologic unit, and an animal colony. An experimental ward of 25 beds has been established. This laboratory is a joint project of the



The George Williams Hooper Institute for Medical Research, University of California Medical School.

University of California Medical School, the National Cancer Institute, National Institute of Health, United States Public Health Service, and the Department of Public Health, City and County of San Francisco.

In 1913 Mrs. George Williams Hooper presented certain valuable property to the Regents of the University of California for the founding of an institute of medical research, known as The George Williams Hooper Institute for Medical Research, in memory of her husband, a pioneer citizen of San Francisco. A Board of Trustees conferring with the Regents determines the policy of The George Williams Hooper Foundation, and its work is closely correlated with that of the Medical School.

In addition to the hospitals connected with our two medical schools, there are some sixteen hospitals in the city proper, and several Class A hospitals in the Bay Area and peninsula cities adjoining San Francisco.

Airplane view of Letterman General Hospital, Presidio of San Francisco.

Located in the Presidio of San Francisco is the Letterman General Hospital, one of the larger Army hospitals of the United States. It was organized in 1898 during the Spanish-American War. In 1900 a permanent hospital was completed to accommodate 380 patients. During World War I, in 1917 and 1918, the hospital was greatly enlarged. Since 1941 further expansion has become necessary because of the great demands placed on the institution by World War II. All of the specialties are well organized in this hospital; the ability and standards of the medical officers in charge of the departments and services are of a high order. A new development resulting from the last war is a center for amputees occupying a portion of the hospital. The Occupational Therapy Department is an especially notable and valuable adjunct in the rehabilitation work, which is such an important feature of this institution.

The Veterans Administration Hospital, known as Fort Miley, has a beautiful location overlooking the Golden Gate and the Lincoln Heights Municipal Golf Course. Built in 1934, it has 356 beds for general medical and surgical cases; reconstruction under way will add approximately 75 beds and new laboratories including deep roentgen therapy. The medical service is under the direction of the Deans' Committee, composed of members from the medical schools of the Universities, Stanford and California. This institution is a diagnostic center, admitting problem cases from other western states. In addition to the regular attending staff there are 47 residents in training at present.

Practically every seaport city has a Marine Hospital, but San Francisco has an especially efficient and well-staffed Marine Hospital of about 400 beds, which has an adequate equipment and a reputation for high quality of medical care. The capacity of the institution was considerably increased during the late War, to about 500 beds, in order to care for the Coast Guard, Maritime Training Schools and Merchant Marine. The hospital is accredited for the training of internes and residents.

Franklin Hospital.

There are four important hospitals operated by Sisters of Catholic Orders, in San Francisco. St. Mary's Hospital, the oldest Catholic Hospital in California, was founded by the Sisters of Mercy in 1857. Today it has a Class A rating, supports 375 beds, has 10 internes and 12 residents.

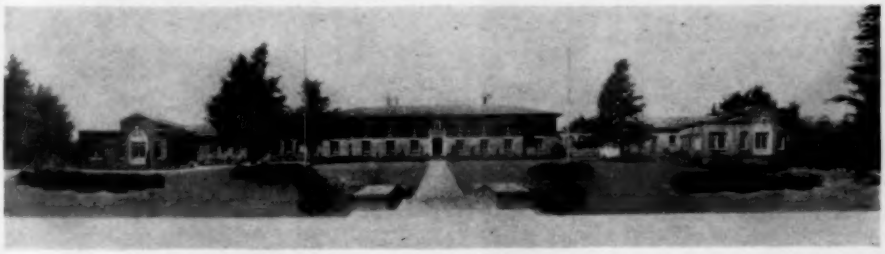
St. Joseph's Hospital was founded by the Franciscan Sisters of the Sacred Heart in 1892. In 1928 a new, modern hospital building was erected on the site of the original hospital. This institution is a Class A general hospital of 235 beds and 45 bassinets.

Mary's Help Hospital is conducted by the Sisters of Charity of St. Vincent de Paul. It was founded in 1906, but was destroyed by the earthquake and fire of that year, and was rebuilt in 1912. Mary's Help is a general hospital, approved by the Council on Medical Education and Hospitals of the

American Medical Association. It has 200 beds, an Out-patient Department, School of Nursing, Cancer Detection Clinic, Pediatrics Department and Physiotherapy Department.

More recently the Sisters of Mercy have taken over the former Dante Sanatarium, which under the original name of the Adler Sanatarium, was for many years the mecca in time of illness of the socially and financially elect of San Francisco. Among the important features were the impeccable trays served to those able to partake of food. During the recent war it was utilized by the Army as a convalescent hospital. On November 4, 1946, the Sisters of Mercy reopened it under the name of the Notre Dame Hospital, for the care of patients suffering from internal medical ailments. The capacity at present is 175 beds.

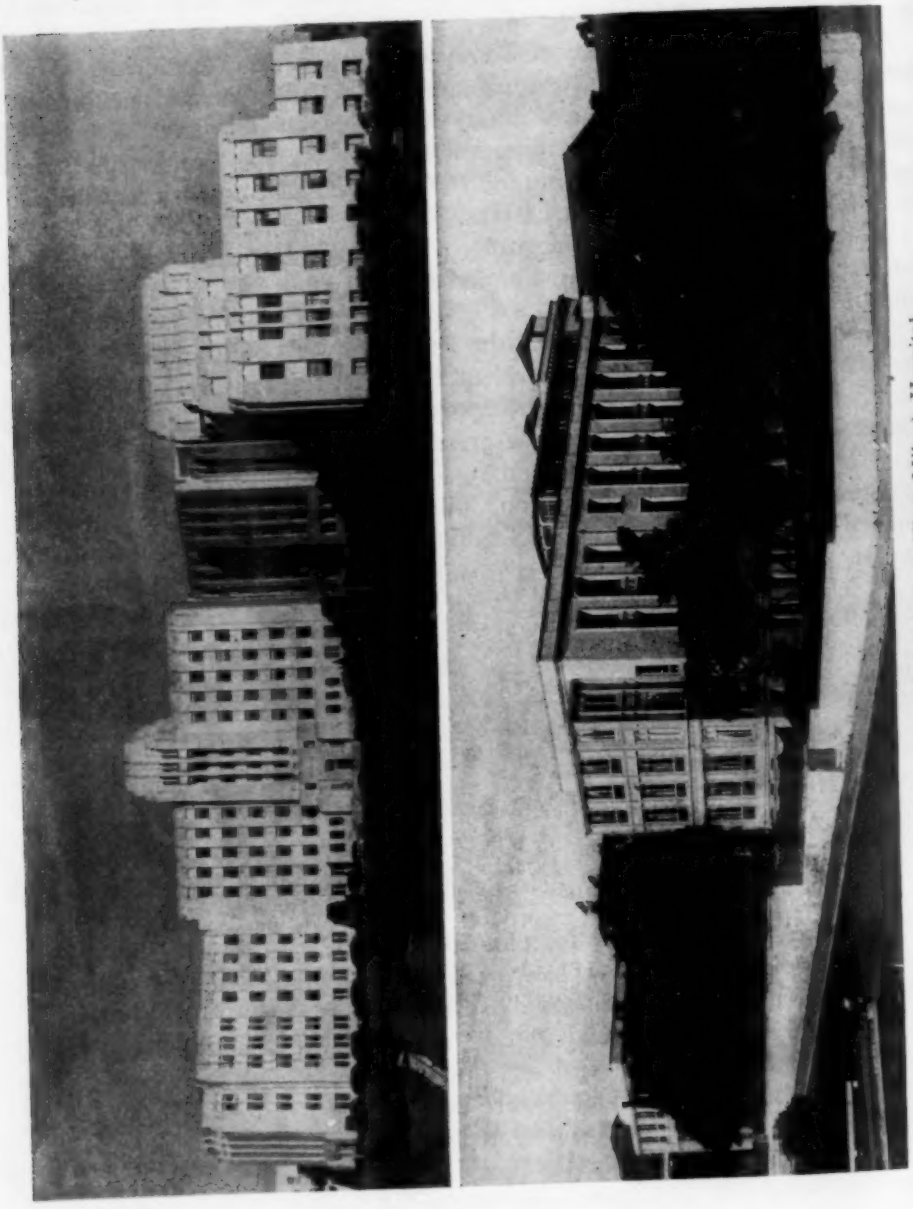
Two hospitals, the French and the Franklin, were built and operated by the French and the German Benevolent Societies, respectively. The former is a modern and complete hospital of approximately 250 beds. The Franklin Hospital was founded in 1852; the present structure was built in 1908 but has been extensively improved and re-equipped since 1939. The hospital has been approved by the American College of Surgeons and the American Medical Association for graduate training in the medical and surgical specialties.



Shriners Hospital for Crippled Children.

St. Luke's Hospital was founded in 1871 by the Reverend Thomas Woodley Brotherton, M.D., D.D., who received his medical training in Baltimore, and came to California in 1849. The present buildings were erected in 1911, but the medical staff of the hospital was well organized and held regular meetings for several years previous to 1911. The staff rosters contained the names of men who were outstanding pioneers in medicine in San Francisco. The hospital is operated under the auspices of the Episcopal Diocese of California. It also is Council-approved for the training of internes and residents, and operates an accredited School of Nursing. About 230 beds are available in this general hospital.

The Southern Pacific General Hospital is an institution of 450 beds, serving approximately ninety thousand employees of the Southern Pacific Railroad Lines. It is a diagnostic center for medical problems and has complete services in all of the specialties. The hospital is accredited for graduate



Top: Veterans Administration (Fort Miley) Hospital.
Bottom: St. Luke's Hospital.

training in internal medicine and general surgery. About 7,500 patients are treated in the hospital annually, together with a large number of patients treated in the Out-patient Department.

The Mount Zion Hospital is a general hospital of about 150 beds, operated by the Federated Jewish Charities of San Francisco. A large number of beds are available for charity patients. In 1931 and subsequently, special research and laboratory facilities have been added. The present hospital was built in 1912; preparations are under way at this time to construct a large, new addition.

San Francisco by the Golden Gate.

San Francisco was one of the cities selected by the Ancient Arabic Order, Nobles of the Mystic Shrine, for erection of a Hospital for Crippled Children. This hospital has a beautiful setting, accommodates 60 patients, with a turnover of about 300 beds per year. Children are able to continue their school work while under treatment, through the coöperation of the Board of Education. The hospital is accredited and has two orthopedic residents and one in pediatrics. There is an affiliation with the University of California Medical School for teaching purposes.

The Hospital for Children and Training School for Nurses has been mentioned as an affiliated hospital of the University of California Medical School. Founded in 1875, it has a present capacity of about 300 beds. An important feature of this hospital is a wing devoted entirely to the care and treatment of communicable diseases. The maternity department and the orthopedic section are also important features of the hospital.

This survey would be incomplete without the mention of San Francisco's vigorous and puissant County Medical Society, which has about 1300 active members. Organized in 1870, the Society purchased its own home on Washington Street in 1926. The large reference library of about 13,000

Bottom: St. Luke's Hospital.

volumes will shortly be distributed to the libraries of the two medical schools. It will be interesting and inspiring (beautiful view) for members of the American College of Physicians to visit the Society's building. It was formerly one of the more pretentious mansions occupied by a pioneer San Francisco family.

Note: Material, including photographs, supplied by the San Francisco Convention and Tourist Bureau and Californians Incorporated, is gratefully acknowledged.